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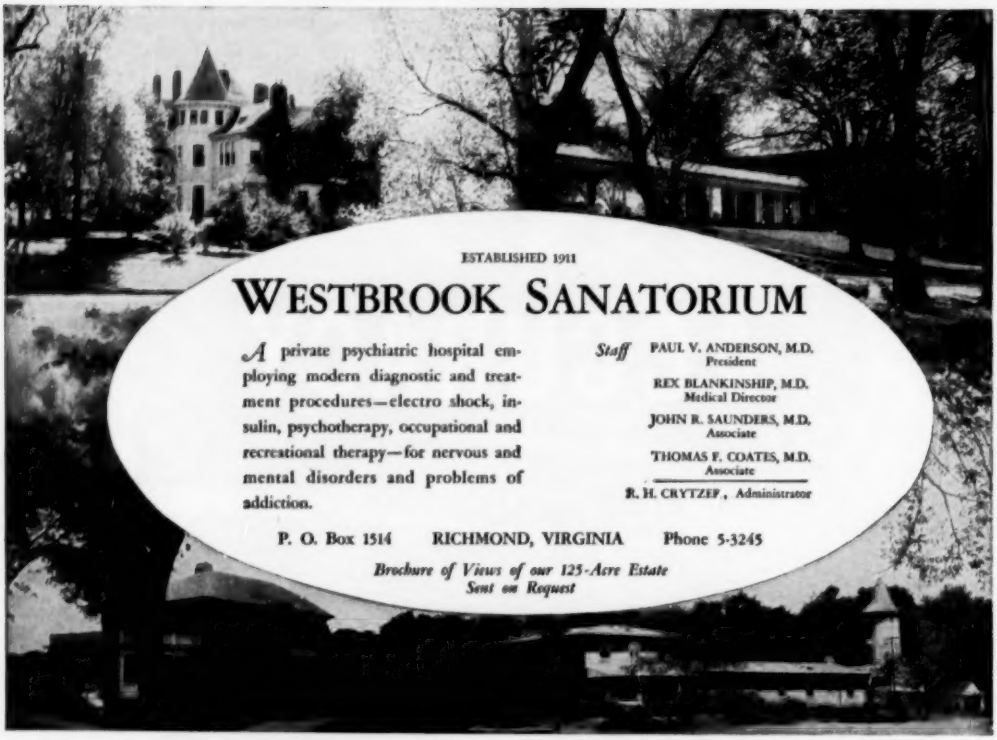
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LANGUAGE PATTERNS IN PSYCHOTIC AND PSYCHONEUROTIC SUBJECTS

MARIA LORENZ, M.D.
AND
STANLEY COBB, M.D.
BOSTON

CLINICALLY, psychological judgments about a person are made in large part through evaluation of linguistic phenomena. The ideas and notions expressed by the patient in talking, or as a response to psychological tests, provide the material from which inferences are made as to his personality. The use of recording devices makes available a permanent record, not only of what the patient says but of the particular manner and form in which he expresses himself. In previous papers on the language of manic [1] and hysteric [2] patients we have tried to show that the form of expression, as well as the content, is psychologically significant. The present paper is an extension of this study of the formal characteristics of language to obsessive-compulsive and paranoid schizophrenic patients.

The composition of the spoken language of an individual or group can be viewed as an equilibrium attained between two tendencies. Statistical properties, grammatical divisions, rules of syntax, and denotative word meaning impose an inherent stability and universality of structure. On the other hand, a certain freedom of selection in arrangement, choice of vocabulary, word frequency, and the connotative use of words appears to be the privilege of the individual. The final crystallization could be expected to reveal the pull of these opposing tendencies and to give a particularizing quality to the language of an individual or group.

In the present paper comparison is made of some of the formal characteristics of language as it is used by groups of individuals contrasting sharply in psychological make-up. The method used is that of tabulating categories of grammar and word frequencies. This method may at first sight appear as a naïve or sterile approach to the complexity of language. A few explanatory statements may perhaps indicate the direction of thought and general perspective that occasioned this counting of words.

It is apparent that despite a relatively fixed range in the structural composition of language, different persons alter the arrangement and frequency of expression as much as the content of their communication. The person who draws attention to himself, or inserts himself into his discourse as a commentator, will shift the bal-

From the Department of Neurology and Psychiatry, Harvard Medical School; the Psychiatric Service, Massachusetts General Hospital (Hall-Mercer Hospital), Boston, and the McLean Hospital, Waverley, Mass.

ance of pronouns toward a preponderance of "I," in contrast to the person who is concerned more with the auditor and draws "you" frequently into the conversation. An elaborate style, in contrast to a simple style, will alter the composition of the language pattern in the proportionate use of "name" words (substantives) and words expressing relationship (verbs) to the use of attributive words (adjectives and adverbs). If a person uses language more for cue and implication than for direct reference, this vagueness may appear reflected in a preponderance of pronominal terms over substantives. The discursive or analytical mind that tends to examine both sides of a proposition will avail itself of more "if's," "and's," and "but's" (conjunctions) than will the mind that tends to see discrete, unrelated parts. The pedantic or circumstantial person will, in a given segment of his discourse, of necessity use a greater number of different words and show an increase in the number of words used once (word frequencies). Categories of grammar and word frequencies can thus be utilized as an index to language habits.

GRAMMATICAL DISTRIBUTION

The form in which a statement is cast involves certain invariables, such as the inclusion of subject and predicate and the presence of connectives and modifying words. Individuals differ, however, in the degree of elaboration, explicitness, vagueness, and habits of limiting or qualifying even a simple observation. Where one person (A) may state simply, "The pen is blue," another (B) will inform you, "The pen which you are holding appears to be blue, doesn't it?" The latter appears artificial and exaggerated, to be sure, but it is a similar tendency which prompts one person (A1) to describe his subjective appraisal of himself as "I'm an optimist," whereas another (B1) indicates, "My weakest point has always been my persistent optimism." The first person makes an observation; the second includes a value judgment with his assertion. In the distribution of parts of speech in a given segment of spontaneous speech, a pattern can be discerned in which individuals B and B1 resemble each other. We can see in this second language pattern a tendency to modify, elaborate, and qualify, as opposed to the tendency of the first pattern (A and A1) to relate the content of thought simply and directly.

WORD FREQUENCY

Similarly, by actual count of words used once and the number of different words in a large segment of speech which includes many sentences typical for A and A1, the expansion and contraction of these vocabularies will tend to fall within a range different from that of B and B1. The number of signs used once and the number of different signs recurring in a segment of speech would reflect the habits of the speaker in using the potential number of signs available to him. The objection may be made that there are individual differences in the size of a person's vocabulary. It is equally true, however, that any two persons matched in intelligence, education, and cultural and social level may differ widely in both the quality and the quantity of words each uses in conveying his meaning. This observation leads to the conclusion that the active vocabulary is to a large extent a function of the psychological differences in the two persons.

TABLE 1.—*Individual 1,000-Word Samplings* Analyzed for Grammatical Distribution and Word Frequencies†*

Individual 1,000-Word Samplings	Substantives					Adjectives					Adverbs				
	N	H	O	M	P	N	H	O	M	P	N	H	O	M	P
1	20.5	14.4	16.6	17.1	16.6	15.5	14.5	13.8	12.7	14.1	15.7	18.0	19.6	16.4	18.5
2	18.9	13.8	16.1	17.0	16.1	14.7	12.9	12.1	12.3	13.9	15.5	17.8	18.9	13.8	15.9
3	18.6	12.5	15.1	16.9	15.1	13.6	12.8	10.9	10.5	12.7	15.3	17.2	18.6	13.7	14.4
4	17.4	11.6	15.0	15.6	15.0	12.7	11.7	10.6	10.2	12.3	13.0	15.0	16.3	12.5	13.9
5	16.9	11.4	14.4	15.1	14.4	12.3	11.4	10.5	9.7	12.1	12.3	14.8	15.3	12.2	13.0
6	16.3	10.6	14.0	14.9	14.0	11.5	10.1	10.3	9.6	12.0	11.4	14.1	14.7	11.1	12.9
7	15.8	10.3	13.8	14.1	13.8	11.4	9.8	9.9	9.1	11.6	11.3	12.8	14.6	11.0	12.8
8	15.7	9.4	13.2	14.0	13.2	10.5	8.4	9.1	8.3	11.0	11.3	12.6	12.9	9.4	12.8
9	14.1	8.2	12.6	13.2	12.6	10.3	8.1	8.8	6.7	10.9	10.2	12.0	12.1	9.1	11.0
10	12.9	8.1	10.4	10.9	10.4	9.1	6.7	7.4	6.5	10.0	9.1	7.9	10.9	8.1	8.6

Individual 1,000-Word Samplings	Main Verbs					Auxiliary Verbs					Pronouns				
	N	H	O	M	P	N	H	O	M	P	N	H	O	M	P
1	15.1	20.4	20.5	18.4	18.5	4.9	7.4	6.9	8.4	6.6	17.6	26.2	21.4	20.6	22.1
2	14.4	20.3	18.0	17.6	17.1	4.6	7.1	6.1	8.3	5.7	16.9	26.0	21.3	20.2	20.7
3	13.7	19.1	17.9	17.0	16.5	4.6	6.9	6.0	6.9	5.3	15.3	25.6	21.1	20.2	17.8
4	13.3	17.8	17.9	16.8	16.5	4.3	6.8	6.0	6.5	5.1	14.5	24.0	20.9	19.4	16.5
5	13.2	16.5	17.2	16.2	16.3	3.9	6.7	6.0	6.3	5.1	14.2	22.0	20.3	18.8	16.5
6	12.6	15.7	16.4	16.1	16.1	3.5	6.4	5.9	5.8	4.7	14.1	20.4	20.2	18.4	15.5
7	12.6	15.7	16.3	15.0	15.8	3.4	6.3	5.8	5.3	4.4	13.0	20.3	19.8	17.7	15.2
8	12.3	15.6	16.0	15.0	15.4	3.4	6.1	5.8	5.1	4.4	10.9	18.6	16.0	17.1	14.6
9	12.0	15.3	15.8	14.6	14.3	3.3	5.9	5.5	5.0	4.0	10.7	18.2	14.3	16.0	14.5
10	11.0	11.5	14.8	13.9	14.2	2.5	5.6	3.1	4.2	2.9	10.5	17.9	13.7	13.9	13.8

Individual 1,000-Word Samplings	Prepositions					Conjunctions					Articles				
	N	H	O	M	P	N	H	O	M	P	N	H	O	M	P
1	12.1	7.7	9.9	11.1	9.3	11.9	9.7	8.8	9.7	11.9	8.2	6.5	7.5	7.6	6.6
2	11.7	7.4	9.6	10.4	9.2	11.5	9.1	8.7	9.5	8.5	7.4	5.1	6.8	6.6	6.4
3	11.1	7.1	9.2	9.9	9.1	10.4	7.9	7.9	8.6	8.2	7.2	4.8	5.7	6.4	6.3
4	11.1	6.6	8.5	9.0	8.2	10.3	7.7	7.2	7.9	7.8	7.2	4.8	5.6	6.3	6.0
5	10.7	6.2	8.4	8.4	7.9	9.5	7.3	6.9	7.1	7.4	6.2	4.7	4.6	6.0	5.1
6	10.3	6.2	8.2	8.3	7.2	8.5	7.0	6.8	7.1	6.5	6.1	4.7	4.5	5.8	5.0
7	9.7	5.6	7.1	7.1	7.1	8.2	5.6	6.6	7.0	6.3	5.5	4.3	3.6	5.5	4.8
8	9.6	5.5	6.9	6.8	7.1	7.0	5.1	6.4	6.4	5.7	5.5	4.0	3.4	5.3	4.3
9	8.8	5.0	6.4	6.4	6.8	6.0	4.9	5.1	5.9	5.3	5.2	3.6	3.3	5.2	3.9
10	8.6	4.3	6.3	6.0	2.7	5.8	4.2	3.9	5.7	4.3	5.1	3.4	3.1	3.8	3.6

Individual 1,000-Word Samplings	Interjections					C/A Ratio					V/A Quotient				
	N	H	O	M	P	N	H	O	M	P	N	H	O	M	P
1	7.0	3.3	3.4	4.1	6.7	1.65	1.30	1.41	1.22	1.60	1.21	2.80	2.77	2.13	1.85
2	5.8	3.1	3.1	3.8	4.9	1.31	1.30	1.32	1.16	1.42	1.17	1.90	2.03	1.90	1.43
3	3.1	2.6	2.8	3.0	4.8	1.27	1.20	1.26	1.14	1.38	1.17	1.90	1.97	1.81	1.41
4	2.5	0.9	2.5	2.1	3.7	1.21	1.20	1.24	1.14	1.28	1.11	1.60	1.73	1.68	1.40
5	1.8	0.4	2.3	2.0	3.2	1.21	1.20	1.23	1.12	1.26	1.10	1.50	1.58	1.67	1.38
6	1.1	0.3	2.0	1.5	2.8	1.15	1.10	1.18	1.07	1.24	1.07	1.40	1.52	1.65	1.31
7	0.8	0.3	1.1	0.5	1.6	1.00	1.10	1.05	1.05	1.20	1.05	1.30	1.50	1.64	1.26
8	0.6	0.3	0.6	0.1	1.0	1.08	1.10	1.05	1.04	1.18	1.01	1.20	1.49	1.62	1.26
9	0.4	0	0.3	0.1	0.8	1.02	1.10	1.00	1.02	1.11	0.98	1.10	1.44	1.45	1.17
10	0.4	0	0.1	0	0.3	1.03	1.10	1.00	0.99	1.02	0.97	0.98	1.07	1.43	1.02

Individual 1,000-Word Samplings	Use of "I"					No. of Words Used Once					No. of Different Words				
	N	H	O	M	P	N	H	O	M	P	N	H	O	M	P
1	94	205	121	95	101	254	199	248	226	238	385	357	374	342	388
2	91	114	118	95	80	244	196	192	218	232	385	315	336	342	352
3	80	110	107	82	77	219	152	173	192	210	361	308	318	317	338
4	70	100	103	79	69	206	150	157	189	199	355	284	294	316	338
5	64	95	95	65	68	200	149	150	184	180	345	282	285	320	333
6	62	88	85	64	67	188	149	141	178	174	329	278	269	309	316
7	54	70	80	61	59	181	144	138	168	159	328	277	263	315	286
8	51	64	67	55	57	173	142	134	168	153	316	273	256	311	289
9	50	57	59	50	35	168	132	125	161	123	312	270	239	310	288
10	46	38	46	46	34	166	124	120	147	122	302	244	211	274	267

* N indicates "normal"; H, hysteric; O, obsessive-compulsive; M, manic; P, paranoid schizophrenic; C/A, conceptual-articulatory ratio, and V/A, verb-adjective quotient.

† Values are expressed as percentages.

MATERIAL, METHOD, AND OBSERVATIONS

The patients selected present a cross section of the population of five groups roughly comparable in social, cultural, and educational level. Analysis was made of recorded, transcribed interview material of the spontaneous production of 10 subjects in each group. Samples of 1,000 words of consecutive speech were analyzed. Obviously, considerable latitude existed in the choice of content material. Insofar as it was possible, each subject was encouraged to talk uninterruptedly and freely about himself so as to obtain a reflection of the preoccupying trend of thought. The "normal" group were requested to reflect upon themselves. The patients, especially the psychotic group, were not specifically guided, but in all instances material was

TABLE 2.—*Grammatical Distribution and Word Frequencies, on the Basis of Ten 1,000-Word Samplings for Each Group*

	Normals, %	Hysteric		Obsessive-Compulsive		Manic		Paranoid Schizophrenic	
		%	P	%	P	%	P	%	P
Substantives	16.7	**11.0**	**<0.01***	**10.9**	<0.01*	14.9	0.1-0.05	14.1	<0.01*
Adjectives	12.2	11.6	<0.01*	10.3	<0.01*	**9.6**	0.02-0.01*	12.0	0.7-0.6
Adverbs	12.5	14.2	0.1-0.05	**15.3**	<0.01*	11.7	0.5-0.4	13.4	0.1-0.2
Main verbs	13.0	16.8	<0.01*	**17.1**	<0.01*	16.1	<0.01*	16.1	<0.01*
Auxiliary verbs	3.8	**6.5**	<0.01*	5.7	<0.01*	**6.2**	<0.01*	4.8	0.8-0.7
Pronouns	13.8	**21.9**	**<0.01***	**18.9**	<0.01*	18.2	<0.01*	16.7	<0.01*
Prepositions	10.4	**6.2**	<0.01*	8.0	<0.01*	8.3	<0.001*	7.5	<0.01*
Conjunctions	8.9	**6.9**	**<0.01***	**6.8**	0.05-0.02*	7.5	0.2-0.1	7.2	0.02-0.01*
Articles	6.4	**4.6**	**<0.01***	**4.8**	<0.01*	5.9	0.3-0.2	5.4	<0.01*
Interjections	2.4	1.1	1.0-0.5	1.8	0.5	1.7	0.5-0.4	2.9	0.5
C/A ratio	1.19	1.12	1.0-0.5	1.17	0.8-0.7	1.09	0.3-0.2	1.27	0.1-0.05
V/A quotient	1.07	**1.70**	**<0.01***	**1.71**	<0.01*	1.68	<0.01*	1.35	<0.01*
Use of "I"/1,000	66	**94**	**0.05-0.02***	**88**	<0.01*	69	<0.05*	65	0.9-0.8
Number of words used once/1,000	200	**154**	**<0.01***	**159**	<0.01*	183	<0.05*	178	0.1-0.05
Number of different words/1,000	341	**289**	**<0.01***	**284**	<0.01*	315	0.05-0.02*	320	0.1-0.05
Ten most frequently used words	I, and, the, to, a, of, in, that, my, was	I, and, the, to, a, of, *if*, that, *is*, *you*		I, and, the, to, a, of, *if*, that, *is*, was		I, and, the, to, a, of, in, that, *if*, was		I, and, the, to, a, of, *if*, that, *he*, *is*	

P denotes probability value by the "*t*" test.
* Statistically significant differences as compared to "normal" values.
Boldface indicates greatest deviation from "normal" value.

selected which appeared to be a spontaneous reflection of their mental content. Only those patients whose language ability retained coherence and grammatical form were included in this series. No one group can be said to serve as a "control" in the usual sense. "Normal" here more correctly means a nonspecific or random group, in contrast to the other groups, which were selected on the basis of similarity in psychological characteristics. It was assumed that significance, if any, would lie in the difference in pattern of the various groups as these patterns compare and contrast.

One of the difficulties presented by these observations is to separate those facts which have intrinsic value from those which, even if statistically significant "facts," are likely to be artifacts. In this material it appears at first sight that all groups of persons who are neurotic or psychotic use more verbs in their language habits than do the so-called "normals." This would seem to be not only logically unlikely (all persons spoke in sentences which ordinarily include subject and predicate), but questionable from the common-sense point of view. It is much more likely that

"normals" appear to use fewer verbs because, in counting 1,000 words, an arbitrarily limited sampling of language which is richer in modifying and discriminating words would in actual count allow for fewer verbs. A further element to be taken into account is that some of the articulatory words (connectives, prepositions) are less apt to be governed by choice when a sample is arbitrarily limited to 1,000 words than by the exigencies of language structure. They may reflect a relative rather than an absolute change, depending upon the emphasis given to use of conceptual words.

Table 1 represents the detailed pattern of language for each group.

Table 2 represents a statistical analysis of Table 1. Comparisons are made with the "normal," or "indeterminate," group, and statistically significant differences are noted.

Results are based on those values in Table 2 which (*a*) show evidence of statistically significant differences from the "normal," or "indeterminate" group and (*b*) represent the greatest variation from the "normal."

RESULTS

The following observations appear to be significant.

A. The conceptual-articulatory ratio remains constant. This ratio reflects the stability of the structure of language—a balance within narrow limits is maintained between words having significance and carrier words, irrespective of speaker or content.

B. Studies of the use of different parts of speech gave the following findings:

I. A general decrease in use of substantives is noted in all patient groups, being most marked in the two neurotic groups. The neurotic patients seem to use the highest number of pronouns and place the greatest emphasis on "I."

II. The use of adjectival modifiers is lowest in the manic group. The obsessive-compulsive group is the greatest adverb user. The language of paranoid schizophrenics remains closest to that of the "normal" in the use of both modifiers.

III. In all patient groups a greater emphasis is put upon use of verbs. The obsessive-compulsive shows this pattern to a marked degree. In all groups the verb-adjective quotient is high, being lowest in the paranoid schizophrenic.

IV. The use of connectives (conjunctions and prepositions) tends to be lower than "normal" for all groups. Articles also appear to be less frequently used. The hysteric appears to use the fewest prepositions. Hysteric and obsessive-compulsive groups use fewer conjunctions and articles than the psychotic group.

C. Word frequency studies gave the following findings:

I. Constrictions of language flexibility are highest in the two neurotic groups (number of different words, number of words used once).

II. In the 10 most frequently used words all groups introduce additional pronouns. The hysteric introduces the second person singular; the paranoid schizophrenic, the third person singular. Some shift in the tense of verbs is noted. The manic group favors the past tense. The hysteric and paranoid schizophrenic groups favor the present tense, while the obsessive-compulsive uses both forms freely.

COMMENT

The substantives indicate the universe of discourse in which a speaker operates. They provide the ideational content of any given segment of speech. In a monologue they may perhaps be used as a very rough approximation of the contextual material in contrast with relationships expressed (verbs) or attributes (adjectives) assigned to content. The quantitative significance standing alone has perhaps little value, but it gains in significance as soon as this value is compared with some other quality in the pattern of speech. For example, in a pattern where "name" words are essentially high in the group and adjectives relatively low, the adjective-substantive ratio thus expressed allows translation into a meaningful statement. Namely, the speaker for some reason does not qualify or differentiate or discriminate the thought content as much as might be expected. This pattern holds true for all groups when compared with a "normal" segment of population, and is most sharply apparent in the manic patient. This verifiable quantitative observation gives some objective support to the descriptive clinical impression that, by and large, manic patients are factual rather than descriptive in their reports. Further, if one considers that adjectives generally used in speaking convey subjective coloring, the relatively low use of adjectives by this group also supports the impression of lack of strongly introverted or subjective attitudes in the manic patients.

The role of pronouns in speech patterns may be threefold. The pronoun may stand for the specific concept of the "I." Other pronouns, such as "it," may substitute for a subject name which frequently recurs in the conversation. The use of "I," "that," and "those" to point to, or emphasize, a statement made is somewhat different from the use of the same word as a substitute for a name. An example of this use is the sentence prefaced with "I think," "I feel," etc., where the focus of attention is divided between the agent and the actual content of the thought or feeling. It is not unlikely that a naïve narcissistic person may say a great deal about himself without specifically using "I" with much frequency, whereas the egocentric person divides his attention between the content and himself. The neurotic patient appears to operate in this fashion: "I" is used with great frequency and tends to subtract emphasis from the subject matter and place it upon the person speaking. It is of interest that the paranoid group leans less heavily upon this device than do the other groups.

Pronouns may also serve as a simple index of the fixation of the speaker around a given focus. Both neurotic and psychotic groups show less tendency to move in their thought processes away from a given point. The paranoid schizophrenic patients appear less rigidly fixed around an area. Observation that "it" occurs among the 10 most frequently used words in all groups also suggests a preoccupation with, or fixation at, a given theme.

The use of modifying parts of speech, adjectives and adverbs, also shows a pattern which is not inconsistent with certain psychological traits of the groups. The pattern of the manic group with respect to adjective use has already been discussed. The obsessive-compulsive person appears as the most habitual adverb user. Adverbs, by contrast to adjectives, are apt to be more objective elements of speech. They convey attitudes of qualifying relationships or actions rather than of things.

Adverbs do not reflect feeling and subjective coloring as much as they indicate attitudes that involve judgments of a less personal sort. A person who automatically is attentive to quantity, degree, differences, and comparisons would tend to introduce adverbs into his pattern of speech. The obsessive-compulsive patient conforms to this pattern.

The significance of verbs in language patterns is less easily divorced from content. Obviously at least one verb is required to express a relationship. It appears in our findings that more verbs are used by both neurotic and psychotic patients than by the "normal" group. But this characteristic may well be an artifact and reflect only a less elaborate sentence structure on the part of these patients than on that of the "normal."

The obsessive-compulsive patient, however, appears to lean heavily on verbs; two verbs appear in his 10 most frequently used words. This pattern, together with the fact that verb modifiers are also highest in this group, suggests that the obsessive-compulsive patient is preoccupied with actions and relationships and the exact quality of the relationship.

The verb-adjective quotient has been used by other workers [3] as an index of anxiety, a high ratio indicating more anxiety. All four of our clinical patient groups showed a significantly higher ratio than did the "normal" group. Johnson [4] suggested a study of vocabulary flexibility by using the ratio of different words to total words. Fairbanks [5] applied this type-token ratio to the language of schizophrenics and concluded that in these patients vocabulary flexibility was decreased. In a grammatical analysis of schizophrenic language this author found a decrease in the use of nouns, prepositions, conjunctions, and articles and an increase in the use of pronouns and verbs. Our results support this evidence but indicate that interpretation of these observations is dependent upon changes noted in other psychotic and neurotic groups.

There is some variation in the pattern of distribution of the remaining articulatory words. Prepositions, articles, and conjunctions appear consistently to be used less frequently by the patient groups than by the "normals." Again, it must be pointed out that changes in the number of articulatory words may be of little significance, since they may reflect only relative change, determined by the sample rather than by the habits of the speaker.

The quantitative aspects of a person's vocabulary seem to be significant. The two neurotic groups stand out distinctly in their use of fewer different words and fewer words only once. A language pattern of many different signs with few recurrent signs points to a high degree of variation and flexibility in using language and little tendency to repetition. A pattern of fewer different signs with frequent recurrence of any one sign reflects a monotony and repetitiveness of language habits. This characteristic is the one shown by the neurotic groups, and to a less extent by the manic group.

It can thus be seen that on the basis of language patterns each group shows some distinctive feature which is open to psychological interpretation. Habits of speech seem to reflect habits of orientation toward the self, external objects, and reality. As a consequence, groups of persons who show certain psychological traits strongly will, when they speak, show similar tendencies in their use of language. If a group

diverges from the norm far enough to be called "neurotic" or psychotic," it will probably fall into one of the convenient types of reaction that we recognize as "diagnoses." To this extent we can look upon an analysis of a sample of language as a diagnostic aid. A few preliminary attempts have been made at such analysis. A sample of language has been taken from a recorded interview, typed out, and studied. An estimate of personality factors has then been made and written out for staff meeting or other clinical use, in much the same way as a psychologist reports the results of a Rorschach test. In the few instances so far attempted the clinical evaluations of the language pattern and of the Rorschach test have shown congruence. This correspondence is striking enough to make one believe that it may be possible to utilize samples of language from recorded interviews to demonstrate certain personality traits.

SUMMARY

The pattern of language habits in terms of grammatical categories and word frequencies has been worked out for two neurotic and two psychotic reaction types. The observations made hold specifically for the 10 subjects in each group, but may be legitimately extended as being representative of tendencies in any such group.

The outstanding characteristics of language patterns were found to be as follows:

The hysteric is distinctive for a tendency to use pronouns with great frequency. The use of "I" predominates and occurs more frequently than in any of the other groups. Emphasis is also given to "you" which appears among the 10 most frequently used words. Substantives are less frequently distributed in the language pattern, being overshadowed by the use of pronouns. In terms of variety of words used (number of different words) and the range (number of words used once) of notions expressed, the language habits appear constricted and static.

Like the hysteric, the obsessive-compulsive patient is a user of pronouns at the expense of substantives. He also greatly emphasizes the "I." His language pattern is especially rich in words expressing relationship (verbs). Two verbs, "is" and "was," appear among the 10 most frequently used words. He relies little on the use of adjectives and stands out from the other groups as the most liberal adverb user. The language pattern closely resembles that of the hysteric in constriction and lack of variety.

The manic patient uses the fewest adjectives. He favors the past tense in verbs. In terms of language flexibility this group is more flexible than the neurotic, less so than the paranoid schizophrenic.

The paranoid schizophrenic group does not stand out as sharply with a specific language habit as do the other groups. Pronouns are less emphasized than in other groups, and "I" is used with relatively the same frequency as it is used by the normal group. In his use of pronouns the paranoid schizophrenic introduces the third person "he" very prominently. The use of adjectives and adverbs approaches most closely that of the normal.

These findings are compatible with and support generally the accepted assignment of psychological traits characteristic of these reaction types. No inference is intended that any language trait is absolutely specific for a reaction type. Instead, the suggestion is offered that language habits may be a broad common denominator, as is any other psychologically determined trait.

The inference drawn from these observations is presented as illustrative of a thesis, namely, that language habits provide a medium for objective and verifiable demonstration of mental attitudes and processes.

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CHRONIC MERCURIALISM

A Cause of the Clinical Syndrome of Amyotrophic Lateral Sclerosis

IAN A. BROWN, M.D.
MINNEAPOLIS

THE COMBINATION of symptoms referable to the pyramidal system, anterior horn cells, and lower brain stem constitutes the syndrome of amyotrophic lateral sclerosis. The literature contains many case reports of this syndrome in which varied etiologic factors have been determined. Wechsler and associates [1] analyzed 81 cases of amyotrophic lateral sclerosis and listed dietary deficiency and inflammatory, vascular, and toxic processes as etiologic factors. This clinical symptom complex has been noted following gastrectomy [2] and polyarthritis,[3] and in triorthocresyl phosphate poisoning.[4] It has recently been considered an atopic-stress disorder, and some improvement has been obtained by the use of adrenocortical extracts.[5] Cord tumors, syphilis, and arachnoiditis may also produce this syndrome. It becomes obvious that the physician in his evaluation of such a symptom complex must seek the clue to the etiology by a careful and detailed search into the patient's occupation, contacts, illnesses, and injuries, since one may uncover a factor which can be successfully treated.

During the past two years we have had occasion to study six cases of chronic exposure to mercury in farmers exposed to Ceresan while dusting oat seeds. All these cases clinically revealed findings of combined motor system involvement. One of these patients died while in the hospital, and we were thus able to carry out detailed pathological studies in this case alone. The purpose of this paper is to present the findings in this fatal case, since the signs and symptoms resembled those seen in amyotrophic lateral sclerosis, even though the etiology was chronic exposure to mercury. This case also illustrates the tremendous toxicity of mercury and its compounds to the central nervous system and should alert the neurologist to the possibility of this type of involvement, particularly when this syndrome appears in a farmer who has been exposed to Ceresan.

REPORT OF A CASE

History of Present Illness.—The patient, a white male farmer, 39 years old, first noted weakness of both arms in June, 1951. Over the ensuing four months there was progressive weakness of all extremities, accompanied by marked atrophy of the muscles of the hands, arms, chest, abdomen, and pelvic girdle, in that order. The rapidly developing weakness prevented the patient from performing his chores and prompted him to seek medical advice. On the basis of the clinical picture and a normal spinogram, a diagnosis of amyotrophic lateral sclerosis was made, and the patient returned to his farm. Two months after returning home he developed complete paralysis of both arms and an inability to walk. Ten days prior to hospital admission he devel-

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oped labored, shallow breathing, which necessitated artificial respiration and the subsequent use of a chest respirator. After this he developed dysphagia, dysphonia, and pooling of secretions in the pharynx. Primarily because of mechanical breakdown of the chest respirator, the patient was transferred to the University of Minnesota Hospitals.

Physical Examination.—The patient on admission was dyspneic, cyanotic, extremely emaciated, and unable to swallow. The oropharynx was overflowing with watery secretions. The patient was afebrile. Examination of the mouth showed swollen, reddened gums and many carious teeth, and a thin dark blue line was readily discernible at the gum margin, particularly around the carious teeth. The posterior pharyngeal wall was infected and swollen. In retrospect, the patient had noted a metallic taste in his mouth several months previously and had noted that the gums were tender.

The blood pressure was 112/80, the pulse rate 96, the heart sounds were normal, and no murmurs were evident. Respirations were feeble, labored, and gasping, and were carried out by accessory respiratory muscles. Diaphragmatic movement was present but feeble.

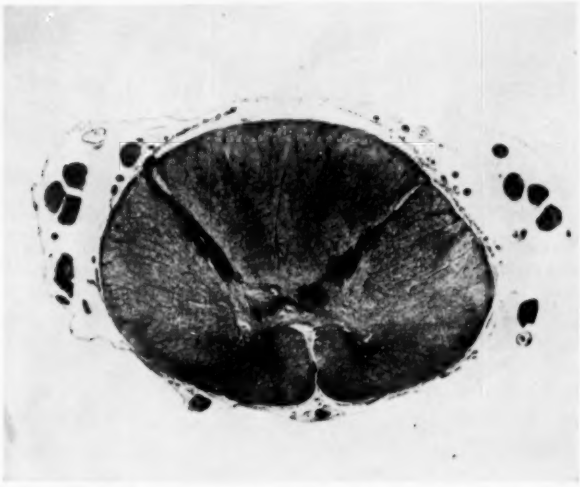

Fig. 1.—Section of the spinal cord showing early demyelination in the lateral columns; Weil stain.

Nervous System Symptomatology.—The predominant symptoms were referable to the central nervous system. The upper cranial nerves showed no abnormalities. Involvement of the lower cranial nerves was evident by dysphagia, dysphonia, and excessive salivary secretions.

The deep reflexes were absent in the upper extremities but hyperactive in the lower extremities with the exception of the left ankle jerk, which was not present. Ankle clonus was present on the right, and knee clonus was obtained bilaterally. A Babinski reflex was present on the left side, and the skin abdominal reflexes were absent bilaterally.

There was extreme wasting of the body musculature, most marked in the extremities. Coarse and fine muscle fasciculations were present everywhere. The patient was able to move his lower extremities, and movements of the arms, except for slight external rotation of the right forearm, were impossible.

The sensory system in all modalities was intact on clinical examination.

Laboratory Findings.—Urinalysis showed no abnormalities. The hemoglobin was 15 gm. per 100 cc.; red blood cells, 4,070,800, and white blood cells, 19,600, with a normal differential count; the sedimentation rate was 23 mm. in one hour. The urinary excretion of mercury was 340 γ in 24 hours. Blood urea nitrogen was 21 mg. per 100 cc.; CO_2 combining power, 105 mEq.; blood

glucose, 104 mg. per 100 cc.; blood chlorides, 116 mEq.; serum proteins, 5.9 mg. per 100 cc.; calcium, 9.6 mg. per 100 cc.; phosphorus, 3.5 mg. per 100 cc.; blood sodium, 141 mEq.; potassium, 5.2 mEq. per liter. The blood Wassermann test was negative. The urinary coproporphyrin excretion was 226 γ per liter, and the urinary excretion of alpha amino acid nitrogen was 68 mg. in 24 hours.

Past History.—The patient was a farmer who had been in excellent health. He had had the common childhood diseases without sequelae and had never had any systemic disease necessitat-

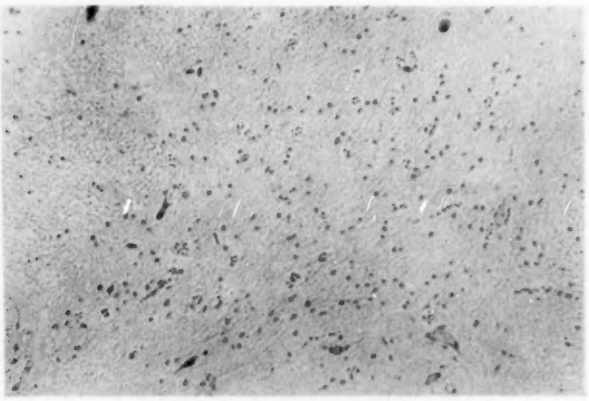

Fig. 2*A*.—Low-power view of the entire anterior horn of the cervical cord, showing almost complete absence of anterior horn cells.

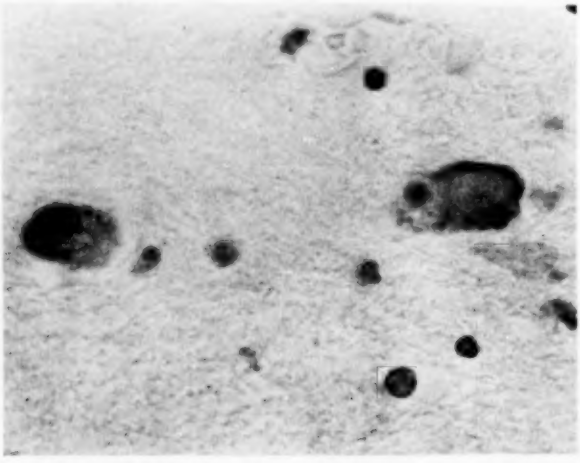

Fig. 2*B*.—High-power magnification of the anterior horn cells of the cervical cord, showing marked chromatolysis and shrinking of these cells. These were the only two cells found in the section of the cervical cord.

ing drug therapy. There was no history of head or back trauma, and the family history was devoid of any hereditary or familial disorders. The patient had, for the past six to seven seasons, dusted his oat seeds with a dusting compound, Ceresan (E. I. du Pont de Nemours & Co.), containing 7.7% mercury in the form of ethylphenyl mercury. The patient had disregarded the

labeled precautions in executing this procedure, which was done by mixing the dusting compound and the seed in an open barrel. No mask was used at any time. He had last performed this act one month prior to the onset of the current illness. There was no history of any other toxic exposure, although the patient did use various insecticides in common use on farms today.

Course in Hospital.—The respiratory involvement and bulbar symptoms upon admission necessitated tracheotomy, and after this procedure the patient was placed in an iron lung. During the ensuing weeks the patient ran a febrile course and respiration was frequently obstructed by mucus. Bronchoscopy was performed on several occasions in order to keep the airways open, and antibiotics were administered. The patient was placed on dimercaprol (BAL, British antilewisite), 1.5 cc. every four hours for two weeks. During this time the urinary mercury excretion rose from 340 to 740 γ in 24 hours, but no clinical improvement was noted. A second course of dimercaprol was given in the same dosage two weeks after the initial course, but again without clinical improvement. The condition of the patient deteriorated over a period of seven months, owing to progressive bulbar involvement. Death occurred eight months after admission to the hospital, after an episode of tracheal obstruction and atelectasis.

Postmortem Examination.—An autopsy was performed two hours after death. No gross microscopic abnormalities were found in the heart, spleen, thyroid, adrenals, or gastrointestinal tract. Bilateral atelectasis was observed in the lower lung fields, and the renal calices contained stones. Microscopic changes were confined to the lungs and liver. A purulent bronchopneumonia was present in the former, and in the latter a moderate degree of midzonal necrosis was evident.

Nervous System.—The chief pathological changes were observed in the nervous system, particularly in the spinal cord.

With the exception of a moderate degree of generalized convolutional atrophy, especially in the frontal lobes, there were no significant alterations of the brain or the spinal cord.

Sections of several cortical areas showed mild vascular changes with some perivascular myelin pallor. There were no neuronal alterations of significance. Sections of basal ganglia and cerebellum were normal. Sections through the brain stem showed pallor and vacuolation of myelin in the pyramidal tracts.

Sections through the cervical, thoracic, and lumbar levels of the spinal cord demonstrated changes in the anterior horn cells and pyramidal tracts (Figs. 1, 2*A* and *B*). The anterior cells were noticeably decreased in number, with complete absence of motor cells in some areas, while at other levels the cells were hyperchromatic and shrunken. The lateral columns exhibited demyelination and vacuolation of a moderate degree.

COMMENT

The syndrome of amyotrophic lateral sclerosis was established by the clinical symptomatology and supported by the pathological changes revealed at autopsy. The presence of large quantities of mercury in the urine established the etiology in this case.

Mercurialism, one of the first-recognized industrial diseases, was known in India in 500 B. C., and mercury stomatitis was described in the first century A. D. In the 16th and 17th centuries, mercury poisoning was common among gilders of gold, silver, and copper. Palsy of the hands, ataxia, paralysis, paresis, loss of teeth, and stomatitis were observed in these victims. Prior to the 17th century most cases of mercurialism were found in the mercury miners. With the introduction of mercury nitrate in the manufacture of fur felt in France (1685), the vast majority of cases of mercurialism appeared in the hatting industry. The colloquialisms "hatter's shakes" and "mad as a hatter" became household phrases and attested to the

unhealthy reputation of the hatting trade. Wright,[6] Neal and Jones,[7] and Smith and associates * reported on a large series of cases of chronic mercurialism in this industry.

Mercury today has many industrial uses. Neal,[10] in reviewing the public health aspects of mercury, listed the following potential sources of poisoning: in mercury mining; in the manufacture of chemicals and alloys; in the production of electric switches, lamps, contact electrodes, furnaces, meters, radio tubes, and batteries; in dentistry, in the making of amalgam fillings and the reclaiming of precious metals; in laboratories, through spillage of mercury from broken thermometers and other mercury-containing equipment; in the manufacture of antiseptics, cathartics, diuretics, disinfectants, bactericidal agents, ointments, insecticides, fungicides, vermicides, explosives, detonators, fuses, percussion caps, and pyrotechnics; in the decoration of china porcelain ware; in photography, printing, engraving; in the production of artificial flowers and imitation jewelry; in the hardening of tools; in the dyeing of woolen goods; in taxidermy and embalming, and in seed treating. The vapor pressure is responsible for the toxicity of mercury, and its dangers are great in laboratories, where often little attention is paid to spilled mercury droplets.

Organic compounds of mercury are as toxic as the free metal. The inhalation of such compounds has given rise to symptoms referable to the central nervous system, including ataxia, dysarthria, altered plantar reflexes, and constricted visual fields.[11] Rats subjected to methyl mercury compounds showed widespread degeneration of the posterior spinal roots, posterior columns, peripheral nerves, and cerebellar cortex. Monkeys under the same exposure showed a diffuse encephalitis resembling that of dementia paralytica.[11] Ethyl mercury compounds are especially toxic to the central nervous system. Hill [12] reported on the death of two stenographers as a result of exposure to ethyl mercury compounds stored in the same office building and pointed out that severe damage may not become apparent for weeks or months after the inhalation of small amounts of mercury.

Little is known about the metabolism and storage of mercury in the body. The liver and kidney are the main storage depots. In seven cases of chronic mercurialism reported by Lundgren and Swensson,[13] the liver and brain contained the largest quantities of mercury. Young, Taylor, and Merritt,[14] noting the similarities in the excretion and distribution of mercury and lead, found mercury quantitatively in the cerebrospinal fluid with all compounds studied but were unable to demonstrate any in the brains of the animals.

Although mercurialism occurs in an acute and a chronic form, the most frequently observed form is that resulting from prolonged exposure to very low concentrations of mercury. The time necessary to produce signs of toxicity varies from 1 to 30 years.

The signs and symptoms of chronic mercurialism, not of nervous system origin, are many. Gingivitis, stomatitis, ptyalism, pharyngitis, otitis, and conjunctivitis are often found. It is not known whether these features are the result of poor oral hygiene or are due to some direct effect of the mercury on the mucous membranes. The excessive salivation could be of bulbar origin. A metallic taste and a dark blue line along the gum margins, similar to the Burton line in lead poisoning, are noted frequently. An erythematous, irregular rash, pallor, and cachexia, the latter often

* References 8 and 9.

very severe, are other features of this condition. Tachycardia and elevated diastolic blood pressure are the most frequently observed cardiovascular signs. Enlargement of the thyroid gland was observed in 6 out of 43 cases by Neal and Jones,[7] and in 33 of 213 cases by Smith and associates.[8] Because of thyromegaly, the clinical manifestations of tremor, weight loss, and tachycardia, the thyroid gland has been regarded as the seat of action of mercury. The basal metabolic rates on this group of patients were not significant. Atkinson[15] reported a brownish-colored reflex from the anterior capsule of the lens which he considered to be an early diagnostic sign of mercury intoxication.

The symptomatology of chronic mercurialism, however, is predominantly of central nervous system origin. The outstanding neurological sign is the tremor, said to be present in all cases of chronic mercurialism. The tremor is bilateral, of fine gradation, and exaggerated on intention and attention. It is most frequently observed in the eyelids, hands, fingers, tongue, cheek, and lips. There are no features which characterize it as specific of chronic mercurialism. Both hypoactive and hyperactive reflexes (often in the same patient), muscle pains, muscle tenderness, fasciculations, dysarthria, and slurred and scanning speech are other neurologic observations. Personality alterations constitute a commonly observed feature of chronic mercurialism. Erethism, a term frequently encountered in the literature and including such personality changes as depression, despondency, easy embarrassment, timidity, excitability, irascibility, and an increasing self-consciousness, is commonly found in chronic mercurialism.

No specific abnormalities of the blood have been noted. Hemoglobin and red cell counts are usually within normal limits. Anemia, eosinophilia, lymphocytosis, albuminuria, and hematoporthyrinuria have also been reported.† Hypercholesteremia was noted in 62% of the cases, according to Smith and associates.‡

Normal persons excrete 0.5 γ of mercury in the urine and 10 γ in the feces daily, according to Stock.[16] Unexposed persons may have as much as 0.1 γ of mercury per 100 gm. of fresh tissue. Mercury may be demonstrated in the urine and feces for months after exposure, the urinary concentration decreasing logarithmically with time. Urinary mercury values are too irregular to be of any value in the determination of the severity of the case. In general, when small quantities of mercury are found in the urine, the inference is made that the mercury has become fixed in the tissues. Signs of toxicity are usually present when 0.1 mg. of mercury is excreted daily, according to Koelsch.[17] The severity of damage to the central nervous system was mirrored only by the concentration of mercury in the spinal fluid, according to Leischner.[18]

Today the use of mercury compounds in the prevention of such diseases as bunt of wheat or smut of barley is a well-established principle of plant hygiene. Ceresan, the seed fungicide used by this patient, and in common use among farmers today, was introduced in 1914 by the I. G. Farbenindustrie. The active ingredient is phenylmercury acetate, present in a concentration of 7.7%. Considerable seed treating is done on farms rather than in the granaries. Schulte § and Ritter and

† References 7 through 9.
‡ References 8 and 9.
§ References 19 and 20.

Nussbaum [21] have emphasized the hazards of treating seed with mercury compounds. In this process the seed is mixed with the mercury compound. It is mechanically mixed by slurry machines in the granaries, but farmers may do this manually and many disregard the use of masks and other precautions. In many instances the "mask" consists of a handkerchief covering the nose and mouth, which at best is very inadequate. Masks used in granaries are readily contaminated by mercury dust. Dimethyl and diethyl mercury compounds are extremely toxic, and the vapors are not readily caught by a gas mask. Farmers are not given sufficient warning about the dangers involved in the use of such compounds. Most successful fungicides used in current farming contain compounds of mercury, arsenic, or cyanides, all of which are toxic to the central nervous system.

The response to dimercaprol, although disappointing in this far-advanced case, was interesting in that it caused a mobilization of mercury and resulted in an increased urinary excretion of mercury. The presence of substantial quantities of mercury in the urine many months after the exposure is to be noted. In some of our less involved cases, the use of dimercaprol appears to have arrested the progress of the illness, and three of the patients have shown no progression of their illness since treatment.

SUMMARY

A case of chronic mercurialism is presented in which the clinical syndrome of amyotrophic lateral sclerosis was found.

In cases of combined motor system disease occurring in farmers, the possibility of chronic mercury poisoning as a result of exposure to Ceresan should be considered.

The hazards of mercury are emphasized.

Chronic mercurialism is a neurotoxic disorder, whereas acute mercurialism is nephrotoxic.

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MÉNIÈRE'S DISEASE

Successful Treatment by Chorda Tympanectomy

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MÉNIÈRE [1] in 1861 described the clinical entity of vertigo, tinnitus, and deafness and predicted that the internal ear would be proved to be the sole site from which these symptoms derived. Not until 1938 was this prediction verified, when Hallpike and Cairns [2] demonstrated histologically a dilatation of the membranous labyrinth in two cases of Ménière's disease.

The two most effective operations for the vertigo in Ménière's disease are differential section of the eighth nerve and total destruction of the labyrinth. The purpose of the former is to preserve the hearing, whereas the labyrinth operation results in total deafness. These operations are designed for unilateral cases, but what if both sides are or become affected? Destruction of both labyrinths would be unthinkable; yet in 10% to 15% of cases the disease is already present or subsequently develops on the supposedly healthy side.

The ideal operation for Ménière's disease should be a minor one, easily and quickly performed, which would abolish the vertigo, yet preserve the hearing and static labyrinth. Such an operation could be done on both sides in bilateral cases. Possibly such an operation may now be at hand in the simple section of the chorda tympani through an ear speculum in the external auditory meatus.

Important questions come to mind. Is the internal ear the exclusive anatomical basis of Ménière's disease? Can severe attacks of Ménière's disease (vertigo, nausea, vomiting, and tinnitus) occur on the side of an already dead labyrinth if deafness and loss of vestibular function are already complete? Clinical observations may shed some light on these questions.

That the chorda tympani nerve might be concerned with sonic and equilibratory functions, as well as taste, first suggested itself in 1947,[3] when the sectioned chorda tympani nerve was used to cover the fenestra in the fenestration operation for otosclerosis. In these cases the severe postoperative vertigo usually present after fenestration was strikingly reduced. This clue led ultimately to section of the chorda tympani nerve in cases of severe paroxysmal vertigo of Ménière's disease. The present study is a report of 97 consecutive cases of Ménière's disease for which section of the chorda tympani nerve was done. In all of these cases operation was done from one to six years ago.

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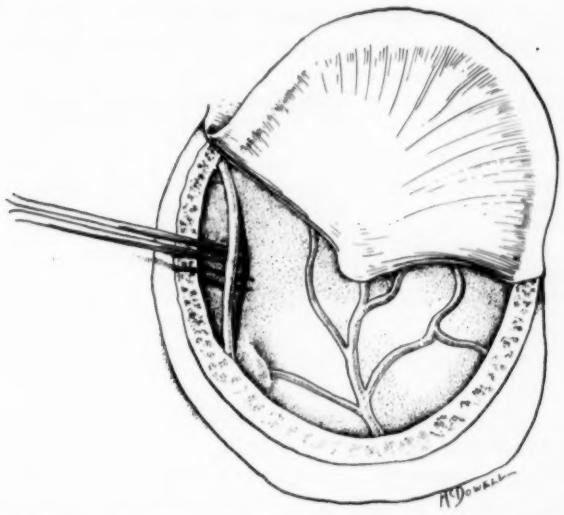
TECHNIQUE

Section of the chorda tympani is done through an ordinary ear speculum in the external auditory meatus with the use of local anesthesia (skin injection of 1 ml. of 1% procaine hydrochloride with three drops of epinephrine chloride 1 : 1,000 or 1 ml. of 2% lidocaine [Xylocaine] hydrochloride with three drops of epinephrine chloride 1 : 1,000). In half the cases preoperative medication consisted of 3 grains (0.19 gm.) of pentobarbital (Nembutal) sodium two hours before operation and 100 mg. of subcutaneous meperidine (Demerol) hydrochloride an hour before operation. In the other half of the cases no preoperative medication whatever was given.

An incision is made from 3 to 9 o'clock through the skin of the posterior wall, floor, and anterior wall of the external auditory canal about 6 to 7 mm. external to the drum membrane. The skin is then reflected as far as the drum membrane. The lower half of the drum membrane is lifted out of its sulcus and folded upward upon itself, thus exposing the chorda tympani nerve (Figure), which is sectioned. The intact drum membrane is then returned to its natural position.



After lifting the drum membrane out of its sulcus, it is folded upward, thus exposing the chorda tympani nerve, which is seen resting on the bipolar electrodes during electrical stimulation. The chorda is then sectioned.

This operation takes about 10 minutes. The skin of the meatus heals in a few days. The patient is ambulatory, on full diet, and leaves the hospital the following morning.

ELECTRICAL STIMULATION OF THE CHORDA TYMPANI

The exposure of the chorda tympani for section afforded an unusual opportunity to study its responses to electrical stimulation.[4]

Stimulation was of three kinds: (1) with a vibration stimulator giving sharp pulses at 120 per second; (2) with a thyratron stimulator capable of giving pulses from very low frequencies to about 500 per second, and (3) with a square-pulse stimulator capable of independent variation of pulse width and strength. This stimulator was used with pulses of 0.3 msec. at frequencies of 50 and 100 cps, and with pulses of 2 and 3 msec. at frequencies of 10, 25, and 50 cps. The purpose of

using these various kinds of stimulation was to determine whether or not it was possible to produce different sensations by different means and to eliminate as much as possible the spread of stimulation.

The results of experimental stimulation of the chorda tympani nerve in 100 cases are shown in Table 1.

In 79 of the cases tinnitus alone occurred with each stimulation. In the 12 cases with vertigo it was described as identical with the vertigo experienced during the attacks. The patients reported hearing with each stimulation tinnitic sounds of hissing, buzzing, drilling, roaring, ringing, or bubbling. Pain [5] was always localized deep in the ear and sometimes referred to the back teeth. The facial muscles contracted with each stimulation of the chorda.

Electrical stimulation of the chorda tympani nerve in 100 cases has not elicited sensations of taste (with or without preoperative medication), even though section of the nerve abolishes taste on the anterior two-thirds of the tongue.

TABLE 1.—*Chorda Tympani Stimulation Responses in One Hundred Cases*

Response	No. of Cases
Vertigo alone	4
Vertigo and tinnitus	8
Tinnitus alone	79
Taste	
Spontaneous	0
Elicited	0
Pain	80
Facial contraction	82

CLINICAL RESULTS

Section of the chorda tympani was done in 97 consecutive cases of Ménière's disease after medical treatment. These patients were in good health and had no evidence of cardiovascular disease, multiple sclerosis, eighth nerve tumor, syphilis, or drug intoxication. The symptoms and findings in these cases varied in degree and consisted mainly in severe paroxysmal vertigo, nausea, vomiting, falling, veering, unsteadiness, fluctuating deafness (average 45 to 50 db.) with lessened bone conduction, varied tinnitus, subjective and objective recruitment, and diplacusis. The caloric tests gave hypoactive responses more frequently than normal responses. Several patients complained of a bitter taste or dryness in the mouth. One patient, when tested, had no taste for bitter, sweet, sour, or salt on the anterior two-thirds of the tongue during the attack of vertigo, nausea, tinnitus, and deafness, which state persisted for two weeks; as the attack of Ménière's disease abated, the taste upon the tongue for all four modalities gradually returned to normal. About 15% of the patients with Ménière's disease have abnormal taste reactions on the anterior two-thirds of the tongue. In 95 of the cases in this report the Ménière symptoms were present for from 1 to 14 years, and in 2 cases for less than 1 year. Both chorda tympani nerves were sectioned for bilateral Ménière's disease in 13 cases. The results of chorda section are summarized in Table 2.

Since section of the chorda tympani 76 (78%) patients are free from major Ménière attacks of vertigo, nausea, and vomiting. Minor attacks seldom incapacitate the patient or keep him from his daily work or activities; they consist mostly in transient momentary giddiness, usually mild, without the violent rotatory vertigo and vomiting which characterized the former attacks. In all of the cases the preoperative hearing was preserved—often useful hearing. Four patients with Ménière's disease have been observed with normal hearing. The tinnitus was lessened in about a third of the cases and disappeared altogether in a few. In many the tinnitus remained conspicuously annoying. None of the patients seem to have been made worse in any way by section of the chorda tympani. During the first few weeks after the operation attacks of vertigo of various degrees of severity occur in about 15% of the cases, but they gradually pass off. Accurate assessment of any treatment for Ménière's disease is difficult, because spontaneous remissions are not uncommon and often a large psychological element is present. Psychiatric, medical, and neurological consultations were obtained whenever they seemed indicated.

In one patient recently operated upon for bilateral Ménière disease, all the steps of the operation were performed on both sides, except that neither chorda tympani

TABLE 2.—*Results of Section of Chorda Tympani in Ménière's Disease*

Duration Since Section of Chorda, Yr.	No. of Cases	Complete Relief from Attacks of Vertigo	Recurrence of Attacks	
			Major	Minor
3 to 6	25	15	5	5
2 to 3	24	11	5	8
1 to 2	48	23	11	14
Total	97	49 (50%)	21 (22%)	27 (28%)

nerve was sectioned. After discharge from the hospital the symptoms of vertigo, nausea, and vomiting continued unabated for several months. The patient was then brought back to the hospital, and this time both chorda tympani nerves were sectioned. After section of both chorda tympani nerves the vertigo promptly disappeared and has not returned.

At the annual meeting of the Otolaryngological Society of Israel in Haifa (1952), Schotz [6] reported nine cases of Ménière's disease in which section of the chorda tympani nerve brought about complete relief from vertiginous attacks. The tinnitus and deafness remained unchanged.

REPORT OF CASES

Two cases of severe Ménière's disease occurred on the side of an apparently dead labyrinth.[7]

CASE 1.—A 50-year-old orderly at Mount Sinai Hospital had total deafness, constant hissing, and roaring tinnitus in the right ear, as well as severe paroxysmal vertigo, nausea, vomiting, and falling. Total deafness was determined by testing the affected ear with both pure tone and speech audiometry, with the normal ear masked at various measured levels of intensity. The static labyrinth did not respond at all to stimulation with ice water. This syndrome, which persisted for four months, followed a skull fracture through the petrous pyramid on the right side. His left ear was normal in all respects.

The right chorda tympani was sectioned over three years ago; after this procedure the vertigo and almost all the tinnitus promptly disappeared and have not recurred.

CASE 2.—A man of 37 had frequent attacks of severe rotatory vertigo, nausea, vomiting, and constant tinnitus in the left ear for three years following an attack of the mumps. There was almost total deafness in the left ear and no caloric response. The patient could not recognize sour, bitter, or salt on the anterior two-thirds of his tongue bilaterally, but he recognized these on the posterior third of his tongue promptly. The left chorda tympani was sectioned 29 months ago, after which procedure the vertigo and almost all the tinnitus promptly disappeared and have not recurred.

In view of these two cases, it seems that the internal ear may not be the exclusive anatomical site for Ménière's disease.

COMMENT

Since stimulation of the chorda tympani nerve produces the sensory phenomenon of vertigo, tinnitus, and pain, this nerve contains afferent fibers other than those for taste. The clinical results in Ménière's disease * following section of the chorda tympani may be explained by assuming functional interconnection between the central nucleus of the chorda afferents (presumably the nucleus of the seventh nerve) and the vestibular nucleus. Abnormal activity introduced into the former by afferents from the chorda tympani are thereby assumed to initiate the abnormal activity of the vestibular nucleus which leads to vertigo. The elimination of the chorda afferents by section abolishes the vertigo in many cases. Other pathways are being investigated and will soon be reported.[11] Testing of this hypothesis, which is thus far based solely on clinical data, must await neurophysiological and anatomical studies. Since this pathway by-passes the internal ear, section of the chorda tympani could explain the abolition of the vertigo and severe tinnitus in the two cases with an already dead labyrinth.

To accept the internal ear as the sole structure responsible for Ménière's disease leads inevitably to destruction of the vital cochlea and static labyrinth, a deprivation which can probably be avoided in a large percentage of cases by section of the chorda tympani. To destroy the labyrinth or perform section of the eighth nerve before trying the simple section of the chorda tympani nerve would seem to reverse scientific order.

Section of the chorda is a simple operation requiring one day's stay in the hospital. It should be done whenever labyrinth destruction or section of the auditory nerve is contemplated, in bilateral cases and in cases in which the vertigo is not yet quite disabling enough for radical surgery.

SUMMARY AND CONCLUSIONS

A new pathway for Ménière's disease is suggested which includes the chorda tympani and its central connections.

Section of the chorda tympani has eliminated the major attacks of vertigo in most of the patients so far treated.

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CARBOHYDRATE METABOLISM IN BRAIN DISEASE

I. Glucose Metabolism in Multiple Sclerosis

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CLAUDE BERNARD'S experiments of a century ago stimulated interest in the relation between functions of the brain and glucose metabolism. Some authors, including Jelliffe,[1] have since reported metabolic abnormalities in multiple sclerosis; the reported changes consisted in a low fasting serum inorganic phosphorus [3] and a high fasting serum cholesterol.[2] More recent studies in patients with multiple sclerosis revealed elevation of the fasting blood pyruvic acid concentrations and an excessive accumulation of this substance following the ingestion of glucose; decreased glucose tolerance and abnormally great and prolonged fall in serum inorganic phosphate were also observed.[4] These workers confirmed earlier reports of a low fasting serum inorganic phosphorus and a high fasting serum cholesterol.

The experiments reported here were designed to elucidate further the nature of metabolic defect already reported to occur in multiple sclerosis. Our studies did not confirm the finding of elevated fasting pyruvic acid concentrations reported by other investigators; however, decreased glucose tolerance was observed, and additional abnormalities in lactic and citric acid metabolism were found.

MATERIALS AND METHODS

Six patients with active multiple sclerosis, ranging in age from 38 to 56, were studied; four of the subjects were men (Appendix). All were free of malnutrition, fever, increased intracranial pressure, and intercurrent disease. All were cooperative during the test. All had a 350 gm. carbohydrate intake daily for three to five days prior to the test. Twenty normal subjects of comparable age served as controls. One subject with a past history of multiple sclerosis but with no present detectable signs or symptoms of the disease was also studied (Case 8).

Blood samples were taken after a 12- to 13-hour fast, and again 1, 2, and 3 hours after the ingestion of 100 gm. of glucose dissolved in 200 cc. of distilled water. Venous stasis and controllable muscular activity were avoided. No anticoagulants were used except for blood glucose and plasma citrate; the red cells were lysed and the proteins precipitated immediately upon collection; the filtrates were kept iced. Determinations were made within four hours after

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collection of the sample. Such precautions are essential; if they were not observed, the concentrations of the small-molecule carbohydrates were altered in directions and degrees that were unpredictable.

The following methods were used: for true blood glucose, the methods of Folin and Wu [5] and Somogyi [6]; for whole blood lactic acid, the method of Barker and Summerson [7]; for whole blood pyruvic and alpha-keto glutaric acids, the method of Seligson and Shapiro [8]; for plasma citric acid, the method of Taussky and Shorr.[9] The precautions observed in the handling of the specimens were those recommended by Friedmann and Haugen.[10]

OBSERVATIONS

Fasting Blood Constituents.—The patients' fasting blood values were normal for true blood glucose, pyruvic acid, and citric acid. The patients respectively had values of 74, 72, 66, 75, 79, and 66 mg. per 100 ml. for true blood glucose; 0.70, 0.98,

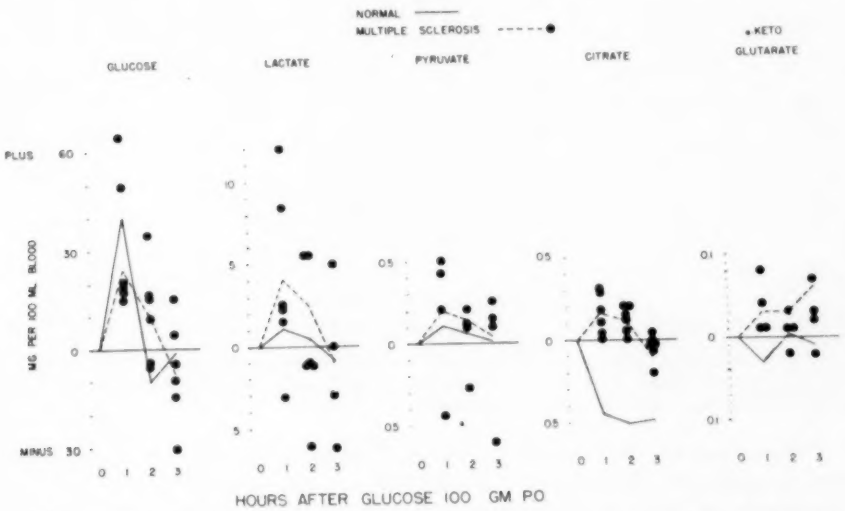

Fig. 1.—Blood constituents after ingestion of 100 gm. of glucose in normal subjects and in patients with multiple sclerosis. Dots indicate individual values in patients; solid line, mean values in normal subjects; broken line, mean values in patients.

0.92, 0.95, 1.44, and 0.63 mg. per 100 ml. for pyruvic acid, and 2.08, 1.47, 1.32, 1.36, 1.35, and 1.93 per 100 ml. of plasma for citric acid. In the normal subjects the mean value for glucose concentration was 74 mg. per 100 ml. (range 60 to 88 mg. per 100 ml.); for pyruvic acid, 0.92 mg. per 100 ml. (range 0.52 to 1.32), and for citric acid, 2.34 mg. per 100 ml. (range 1.6 to 3.6 mg. per 100 ml.).

The patients showed abnormal values for fasting levels of lactic and alpha-keto glutaric acids. The patients had blood lactic acid values of 14.75, 11.00, 13.75, 10.00, 19.00, and 10.00 mg. per 100 ml., respectively, whereas the normal mean lactic acid concentration was 7.4 mg. per 100 ml. (range 2.75 to 11.6 mg. per 100 ml.). The patients' blood alpha-keto glutaric acid levels were 0.19, 0.18, 0.13, 0.15, 0.08, and 0.20 mg. per 100 ml., respectively, whereas the normal mean alpha-keto glutaric acid concentrations was 0.11 mg. per 100 ml. (range 0.03 to 0.17 mg. per 100 ml.).

Carbohydrate Metabolism After Ingestion of Glucose.—The results of the oral administration of glucose in the patients as compared to the response of the control group showed much overlap with regard to changes in blood glucose and in lactic and pyruvic acids. However, the average changes demonstrate significant abnormalities in the patients in every constituent measured except, perhaps, blood pyruvate (Fig. 1). These abnormalities were a lag in the return to fasting concentrations of the true glucose, an excessive accumulation of lactic acid, and a rise, rather than the normal fall, in citric and alpha-keto glutaric acid concentrations. The most consistent and striking difference was in the change in plasma citric acid concentrations after the ingestion of glucose (Fig. 1).

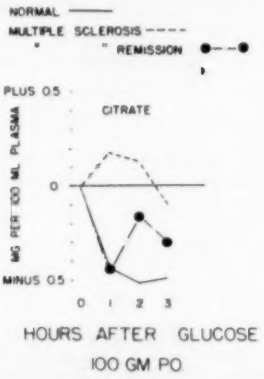

Fig. 2.—Blood constituents after ingestion of 100 gm. of glucose in normal subjects and in two patients with spinal cord disease. Dots and circles indicate individual values in the two patients; solid line, mean values in normal subjects.

The subject who had recovered completely from multiple sclerosis showed normal changes in the blood constituents after ingesting the glucose (Fig. 2).

COMMENT

Although the differences observed between the normal group and the multiple sclerotic patients are not uniformly striking, they are consistent and follow a definite pattern. Moderate impairment of glucose tolerance and perhaps an increased pyruvic acid accumulation reported by other investigators [4] have been corroborated in our study. In addition, the present work reveals increased accumulation of lactic, citric, and alpha-keto glutaric acids after the ingestion of glucose.

The normal fasting pyruvic acid concentrations found here do not confirm earlier reports of high values.[4] However, the methods used were not the same. It is well known that older methods used for determination of pyruvic acid measure varying amounts of alpha-keto glutaric acid also. Seligson and Shapiro's [8] chromatographic technique, which was used in the present study, eliminates this difficulty. The findings of an abnormally high fasting alpha-keto glutaric acid lends support to this explanation of the high blood pyruvate concentrations previously reported by other investigators.[4] The observance of certain precautions in handling of blood in our

study perhaps also explains the discrepancies between our findings and those of elevated fasting blood pyruvic acid levels reported by Jones and co-workers.[4]

The finding of a rise, rather than of the normal fall, in plasma citric acid after ingestion of carbohydrate deserves additional comment. This abnormality was also observed in the present study after intravenously administered dextrose (50 gm. given slowly over a period of two hours) in one patient. Pincus, Natelson, and Lugovoy [11] reported this abnormality in diabetic patients with "neurological symptoms... and abnormal EEG," but not in ordinary diabetic subjects. These authors also observed this abnormality in children with a history of convulsions (Table). In conjunction with the present study, we tested the carbohydrate metabolism after the ingestion of glucose in two patients with spinal cord disease but without organic brain disease. One patient had progressive muscular atrophy, and the other had

Mean Changes in Plasma Citric Acid Concentration after Ingestion of One Hundred Grams of Glucose

Condition	No. of Cases	Authors	Time After Ingestion of Glucose			
			½ Hr.	1 Hr.	2 Hr.	3 Hr.
			Mg. per 100 Ml. Plasma			
Normal	12	Henneman and Altschule	.....	−0.45	−0.51	−0.49
Normal	24	Pincus, Natelson, and Lugovoy [11]	.....	−0.25	−0.55	−0.7
Progressive muscular atrophy	1	Henneman and Altschule	.....	−0.15	−0.47	−0.52
Amyotrophic lateral sclerosis	1	Henneman and Altschule	.....	0	−0.1	−0.3
Multiple sclerosis	6	Henneman and Altschule	.....	+0.17	+0.12	−0.1
Diabetes with neurological symptoms	4	Pincus, Natelson, and Lugovoy [11]	+0.45	0	−0.25	−0.3
Children with seizures	4	Pincus, Natelson, and Lugovoy [11]	.....	+0.44	+0.11	+0.24

amyotrophic lateral sclerosis. The findings in the latter were abnormal only with regard to glucose tolerance (Fig. 3); the changes in plasma citric acid were normal. The patient with progressive muscular atrophy was close to death, and on examination he showed scarcely any skeletal muscle at all; in this patient the blood glucose and lactic and alpha-keto glutaric acid curves were abnormal after the ingestion of glucose, but the changes in plasma citric acid were entirely normal (Fig. 3).

The abnormalities observed in the patients with multiple sclerosis suggest that there is a defect in the utilization of the small carbohydrate fragments in this disease. This defect is not absolute, however, and is only temporary, for the levels of glucose and of lactic, pyruvic, and citric acids return to the fasting values in time. The abnormalities are in no way comparable with those present in diabetes; although diabetic patients cannot utilize carbohydrate normally, they exhibit a normal or decreased elevation of blood lactic and pyruvic acid concentrations and a normal citric acid fall after taking glucose,* findings different from those observed in multiple sclerosis. Malnutrition and starvation in otherwise normal subjects produce the same abnormalities as in diabetes.[14] The patients studied by us, however,

* References 11 through 13.

were well nourished and cooperative regarding the pretest high carbohydrate diet, and, accordingly, malnutrition could not have caused the changes found. The observed abnormality in carbohydrate metabolism appears to be related in some way to brain disease.

SUMMARY

Carbohydrate metabolism in patients with multiple sclerosis is abnormal. Fasting whole blood lactic and alpha-keto glutaric acid concentrations are elevated. After the oral administration of 100 gm. of glucose there is a lag in the return to fasting level of the true blood glucose, an increased accumulation of lactic and

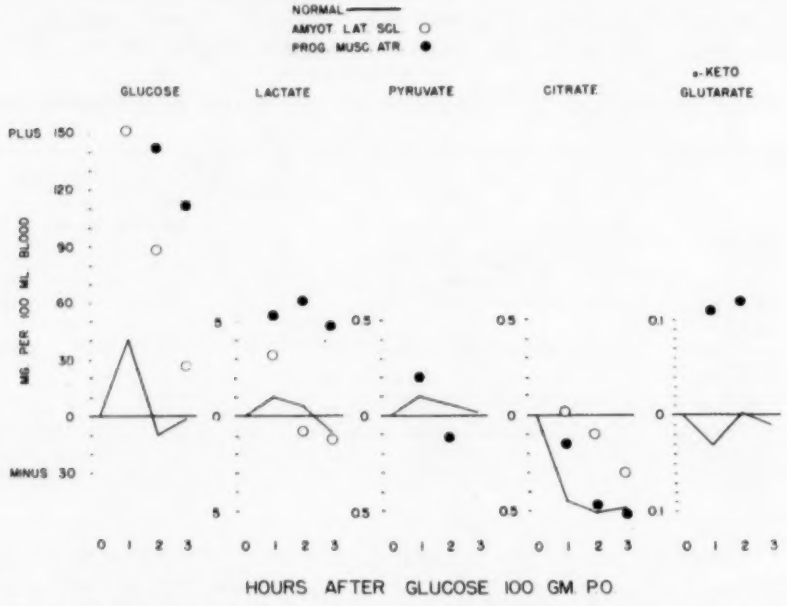

Fig. 3.—Plasma citric acid levels after the ingestion of 100 gm. of glucose in one patient in remission after multiple sclerosis (dots) compared to mean values in normal subjects (solid line) and in patients with multiple sclerosis (broken line).

perhaps pyruvic acids, and a rise, rather than the normal fall, in plasma citric acid and whole blood alpha-keto glutaric acid concentrations.

APPENDIX

Case 1.—M. C., white man, aged 40. Weakness of legs and incoordination ushered in multiple sclerosis in 1941. There was improvement within a year and recurrence a year later, this time with the addition of weakness of the left hand and occasional tremors of the legs. The patient has been studied since August, 1950, when examination revealed minimal nystagmus, slight incoordination of the left hand and leg, and difficulty in starting the urinary stream. There was weakness of the left arm and slight weakness of the left leg, with a marked increase in tonus. Romberg's sign was positive, and Babinski's sign was positive bilaterally. During the three and one-half years of observation the patient's course has shown moderate fluctuations. There has been a slow increase in his urinary difficulties. The last examination showed moderate pallor of the optic discs, dependence on his cane for support, and a slightly bent posture.

Diagnosis: Multiple sclerosis.

CASE 2.—P. D., white woman, aged 34. Onset of multiple sclerosis, in June, 1945, with numbness of right foot gradually spreading over entire right side. She has had two partial remissions, both starting during pregnancy and gaining further momentum during puerperium. Exacerbation in June, 1950, approximately one year after the birth of second child. First clinic visit was in September, 1950. Examinations since then have indicated minor clinical fluctuations. She has had visual disturbances and difficulty in urinary control intermittently. The patient is unable to walk without assistance. There is weakness of both legs and increase of tonus of the lower extremities. Abdominal reflexes are absent. There is bilateral ankle clonus. Babinski's sign is bilaterally positive. Vibration sense is absent below the iliac crests.

Diagnosis: Multiple sclerosis.

CASE 3.—R. G., white man, aged 39. Onset of multiple sclerosis, in 1943, with diplopia and weakness of the right leg. There was a remission within a few months, and the patient was apparently well until 1945, when weakness of the legs recurred. The course has been gradually progressive since that time, with no full remission. The patient was first seen here in March, 1950. Neurological examinations since have shown only moderate fluctuations in the course of the disease. The major difficulty has been moderate weakness of his legs, necessitating the use of an ankle brace and a cane in order to walk. The patient has slight urinary frequency and difficulty in starting the urinary stream. Romberg's sign has been consistently positive, as have been the Babinski signs. Other pathologic toe phenomena, such as Oppenheim's, Rossolimo's, and Mendel-Bechterew's signs, have been present from time to time. There has been a variability in the degree of loss of sensation.

Diagnosis: Multiple sclerosis.

CASE 4.—R. M., white man, aged 34. Onset of multiple sclerosis was in 1939, with diplopia lasting six weeks. In 1944, his Army basic training program was interrupted when he developed a coarse tremor in both hands and urinary frequency, and experienced extreme fatigue. The tremor improved, but was still evident on discharge in 1944. In 1949, after an upper respiratory infection, the patient experienced numbness in both legs extending up to the umbilicus, some unsteadiness of gait, and dragging of the left leg. The numbness disappeared in 1950. The patient has been known to this clinic since January, 1953, and since that time experienced one exacerbation but subsequently improved to the level of his original visit here. He reports that he feels well but becomes fatigued easily. He walks unaided, but with abnormal gait. There is slight to moderate ataxia in coordination tests. Romberg's sign is positive. Right leg shows slight triple flexion weakness. Arm reflexes are increased bilaterally. Cremasteric reflexes are absent. Babinski's sign is positive bilaterally.

Diagnosis: Multiple sclerosis.

CASE 5.†—L. M., white woman, aged 57. Onset of multiple sclerosis was in the fall of 1938, with acute gastrointestinal symptoms followed by weakness and numbness of all extremities. She recovered partially by the following spring. In the next few years she had several brief but very acute episodes of nausea, together with extreme weakness of the extremities accompanied by sensory changes. She improved after each of these exacerbations until 1944. Since that time, according to the patient, she has slowly become worse. She has been known to this clinic since March, 1950. Since then there have been minor fluctuations in her condition, with an over-all slight steady increase in symptoms, in part relieved by slight improvement during the past year. Speech is now slightly dysarthric, and she is able to walk only with the support of another person. Ataxia has increased on the right. She has frequency, urgency, and occasional incontinence of urine. There is weakness of both legs, with snap-lock spasticity of the left leg. Romberg's sign is positive. Babinski's sign is positive bilaterally. There is ataxia in performance of coordination tests, especially on the left, and vibration sense is diminished to absent on the left side.

Diagnosis: Multiple sclerosis.

† Observations were made in this case after completion of the above study. After the ingestion of glucose her blood glucose and lactic, pyruvic, citric, and alpha-ketoglutaric acid levels were all abnormal.

CASE 6.—H. T., white woman, aged 39. Onset of multiple sclerosis, in 1942, with dragging of left leg when fatigued, but with improvement with rest. In 1947, after an operation under spinal anesthesia, both legs became affected. When first seen at this clinic in August, 1948, she was having difficulty in walking, incontinence of urine, diminished visual acuity, and nystagmus. Examination showed slight bilateral temporal pallor and bilaterally positive Babinski sign. Vibration sense was diminished below the knees. In July, 1952, the patient experienced a moderate exacerbation involving her left arm, with a slight increase in gait disorder, a positive Romberg sign. She improved within three and one-half months, had another slight reexacerbation from which she recovered within another six months, and again suffered a slight exacerbation in January, 1954, from which she is again recovering.

Diagnosis: Multiple sclerosis.

CASE 7.—A. T., white man, aged 50. Onset of multiple sclerosis, in 1931, with blindness of left eye for two weeks. Complete absence of symptoms from 1931 until 1937, when the patient experienced numbness of legs. There was partial improvement lasting until 1948, when he suffered paralysis of the left leg which improved partly within the next few months. There was another severe exacerbation in March, 1951. The patient has been known to this clinic since June, 1951. During this time he has shown gradual inexorable progression of symptoms and signs, and at the present time he is severely incapacitated. There is intermittent blurring of vision, and frequency and urgency of urination. He has used a wheel chair since December, 1953, though able to stand and walk a little with great difficulty with the use of canes. Moderate weakness and much increase of tonus are present in arms and legs. Vibration sense is absent from the iliac crests downward.

Diagnosis: Multiple sclerosis.

CASE 8.—B. S., white man, aged 23. Numbness of the right foot, difficulty in going up and down stairs, difficulty in writing, dizziness, and headache ushered in multiple sclerosis in 1950. There was a complete remission in two months, and the patient remained well until seven months later, when vision in the right eye became blurred; there was nystagmus to the left. The residuals of this second attack persisted for a time, but neurological examination became normal in six months. He remained well except for a short period beginning a year later, when minimal temporal pallor of the left optic disc developed and a few nystagmoid movements on left lateral gaze were noted. Recovery ensued and lasted until 10 months later, when visual difficulties again became apparent, with enlarged blind spots, double vision on extreme lateral gaze in either direction, and weakness of the right abducens; there was minimal temporal pallor of the left optic disc, and cremasteric reflexes were absent. In a few months, i. e., eight months before our study, the patient had fully recovered from this fourth attack, remaining entirely well with no neurological abnormalities.

Diagnosis: Multiple sclerosis in remission.

CASE 9.—E. B., white man, aged 51. Onset of illness, in 1943, with fibrillations of the left upper arm and "shrinkage" of left hand, at first without noticeable loss of strength. There has never been any trend toward improvement. When first seen at this clinic in September, 1949, there was marked weakness of the left hand and arm and moderate weakness of the right hand and arm, with atrophy in all. Fibrillations of muscles of both upper and lower extremities were observed. The diagnosis made at that time was progressive muscular atrophy, Aran-Duchenne type. The illness continued its inexorable downward course, and by November, 1953, there was atrophy of the tongue, slurring of speech, marked weakness of the grip of the right hand, paralysis of extension of the right wrist and elbow, paralysis of the left hand and arm, with marked atrophy of all muscles of the shoulder girdle bilaterally and of his arms and hands, with fibrillations. The patient died in February, 1954.

Diagnosis: Progressive muscular atrophy (Aran-Duchenne type).

CASE 10.—N. D., white man, aged 49. The onset of the present illness was in 1952, when the patient noted weakness of his left hand when it was cold. There was gradual increase of disability, and by January, 1954, there was marked weakness of extension and moderate weakness of adduction of the left shoulder. Elbow extension and grip were markedly weak, and elbow flexion moderately weak. There was marked atrophy of the small hand muscles and a slight claw-hand deformity of the left hand. On the right there was slight weakness of the grip of the hand and beginning of claw-hand formation. There were marked muscular fibrilla-

tions of the arm and shoulder muscles bilaterally. Coordination tests could not be performed with the left hand, and the Mayer reflex was absent on the left. Neurological examination was otherwise within normal limits.

Diagnosis: Amyotrophic lateral sclerosis.

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CARBOHYDRATE METABOLISM IN BRAIN DISEASE

III. Fructose Metabolism in Schizophrenic, Manic-Depressive, and Involutional Psychoses

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STUDIES made in this laboratory have demonstrated that abnormalities in the intermediary metabolism of orally and intravenously administered glucose occur in patients with schizophrenia, manic-depressive psychoses, and involutional melancholia.[1] These defects appear to constitute a metabolic error that impairs the peripheral oxidation of the small carbohydrate fragments. There has been no thorough investigation of fructose metabolism in these psychoses, although fragmentary studies have been reported.[2] The metabolic pathways of glucose and fructose are not entirely the same, and, therefore, the intermediary metabolism of fructose in the psychotic patients might not show the abnormalities exhibited when such patients receive glucose.

MATERIAL AND METHODS

The material and methods were the same as those described previously.[1] Pure fructose in doses of 50 or 100 gm. was dissolved in 200 cc. of distilled water and administered by mouth; in other experiments 50 gm. of pure fructose, as a 10% solution, was infused intravenously in one-half hour. Fructose determinations were made by the method of Roe[3]; glucose was calculated as the difference between the sum of glucose and fructose (by the method of Somogyi[4] and Folin and Wu[5]) and fructose alone. Measurements of blood pyruvic acid were all made by the nonchromatographic technique of Friedemann and Haugen.[6] Blood and urine specimens were collected as previously described.[1]

OBSERVATIONS

A. *Effects of Oral Administration of Fructose.*—Measurements of blood fructose and lactic and pyruvic acid and of serum inorganic phosphate concentrations after ingestion of 50 gm. of fructose by two normal subjects and by five psychotic patients (twice by one of them) revealed no differences between the two groups.

The psychotic patients showed an average rise in blood glucose concentration of 8.8 mg. per 100 cc. one-half to one hour after the ingestion of the fructose, in contrast to the steady fall, with a maximal change of —6 and —16 mg. per 100 cc., in the two normal subjects. The changes in serum inorganic phosphate concentration were variable; however, all subjects studied showed a rise above the fasting concentration after the first half-hour.

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When 100 gm. of fructose was given by mouth to five normal subjects and to four untreated psychotic patients (one received it twice), no significant differences in blood fructose concentration were found (Fig. 1). The four psychotic patients

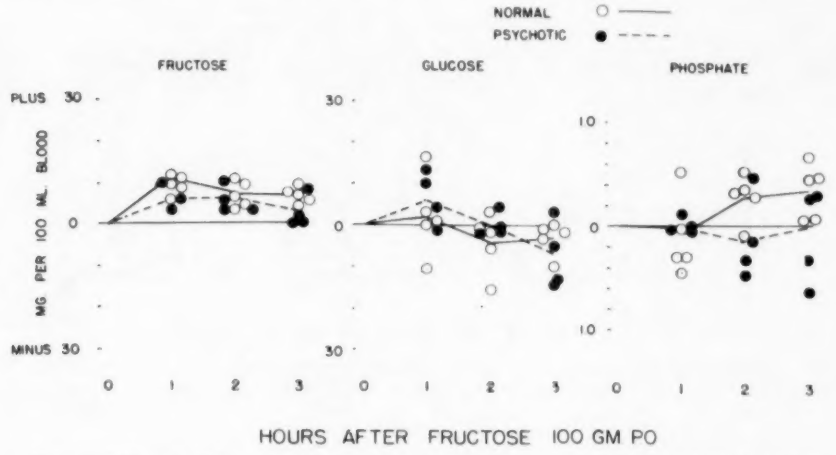

Fig. 1.—Effect of 100 gm. of fructose given by mouth on concentrations of blood fructose, glucose, and inorganic phosphate. Open circles refer to normal subjects. Lines indicate average changes, the broken line indicating changes in psychotic patients.

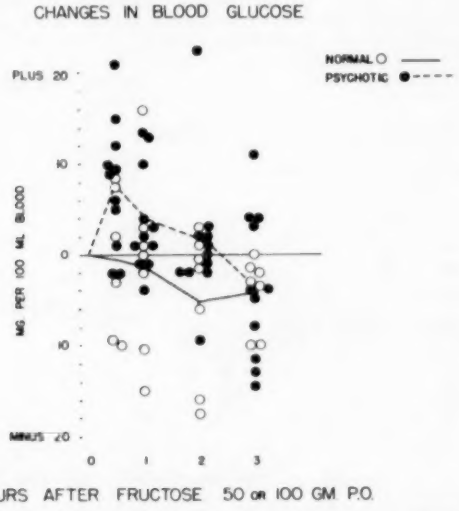

Fig. 2.—Changes in true blood glucose concentration after ingestion of 50 and 100 gm. of fructose. Open circles refer to normal subjects. Lines indicate average changes, the broken line indicating changes in psychotic patients.

showed a slight rise in blood glucose concentration one hour after ingesting the 100 gm. of fructose; this rise averaged 10 mg. per 100 cc. When the changes in blood glucose concentration for subjects who received 50 or 100 gm. of fructose

are combined and are plotted so as to show the changes at one-half hour after ingestion (Fig. 2), the average changes reveal the expected normal fall in the normal subjects, whereas the patients show a slight initial rise; there is much overlapping, however.

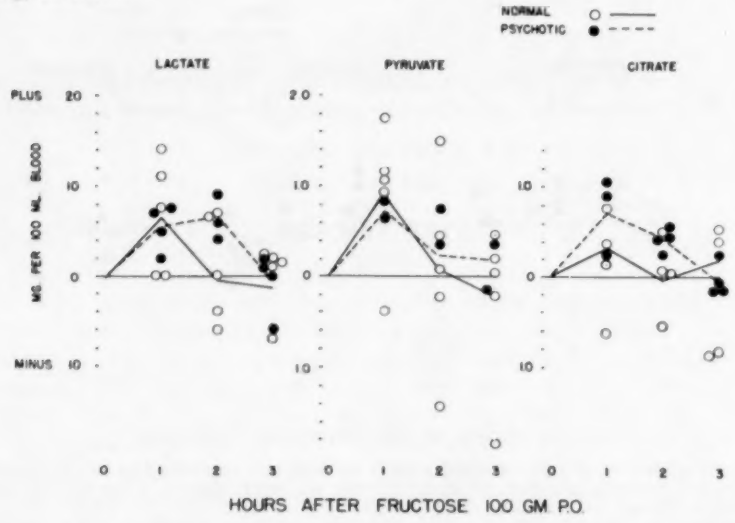

Fig. 3.—Effect of 100 gm. of fructose given by mouth on concentrations of blood lactic, pyruvic, and citric acids. Open circles refer to normal subjects. Lines indicate average changes, the broken line indicating changes in psychotic patients.

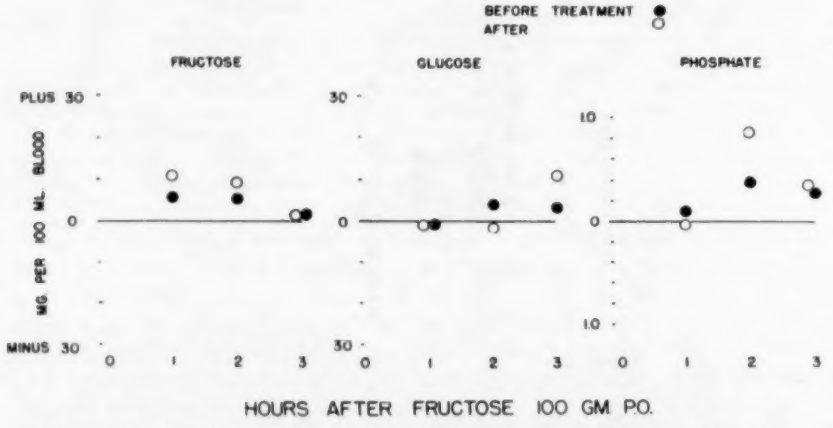

Fig. 4.—Effect of 100 gm. of fructose given by mouth on concentrations of blood fructose, glucose, and inorganic phosphate in one psychotic patient before and after treatment. Open circles refer to changes after treatment.

The serum inorganic phosphate concentration showed no change, or a slight rise, in the normal subjects who ingested 100 gm. of fructose, whereas the serum inorganic phosphate concentration in the psychotic patients showed no consistent change (Fig. 3).

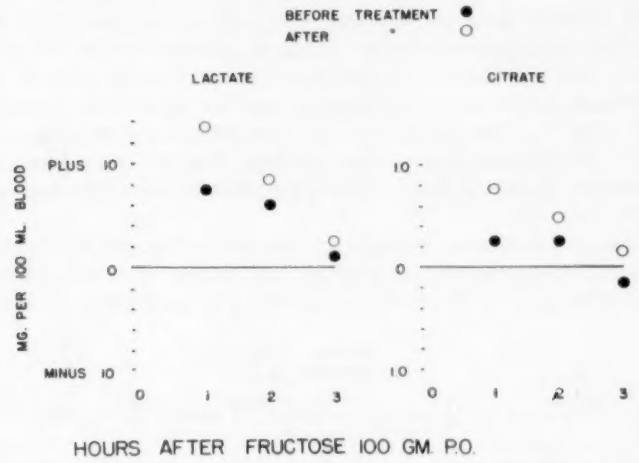

Fig. 5.—Effect of 100 gm. of fructose given by mouth on concentrations of blood lactic and citric acids in one psychotic patient before and after treatment. Open circles refer to changes after treatment.

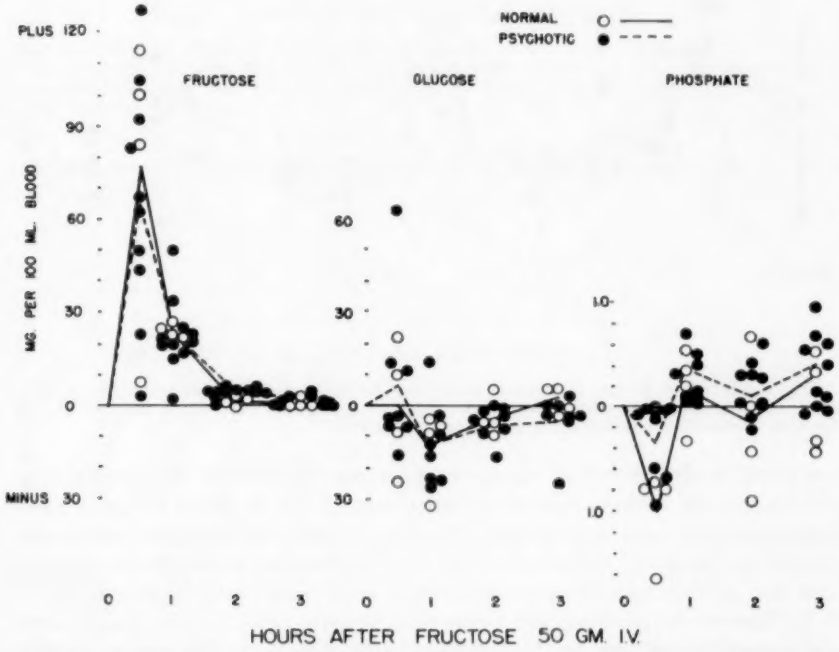

Fig. 6.—Effect of 50 gm. of fructose administered intravenously on concentrations of blood fructose, glucose, and inorganic phosphate. Open circles refer to normal subjects. Lines indicate average changes; broken line indicates changes in psychotic patients.

Changes in blood lactic acid concentration were not significantly different in normal subjects as compared with the psychotic patients, except that the return to the control level was, on the average, slower in the psychotic patients (Fig. 3). Changes in blood pyruvic acid concentration were not significantly different in the two groups (Fig. 3). The plasma citric acid concentration showed larger rises in the psychotic patients than in the normal subjects (Fig. 3); there was much overlapping, however. Treatment had no discernible effect on any of the findings (Figs. 4 and 5).

B. *Effects of Intravenous Infusion of Fructose.*—Changes in blood fructose level after the intravenous infusion of 50 gm. of fructose were remarkably similar in 4 normal subjects and in 12 psychotic patients (Fig. 6). Studies of blood glucose

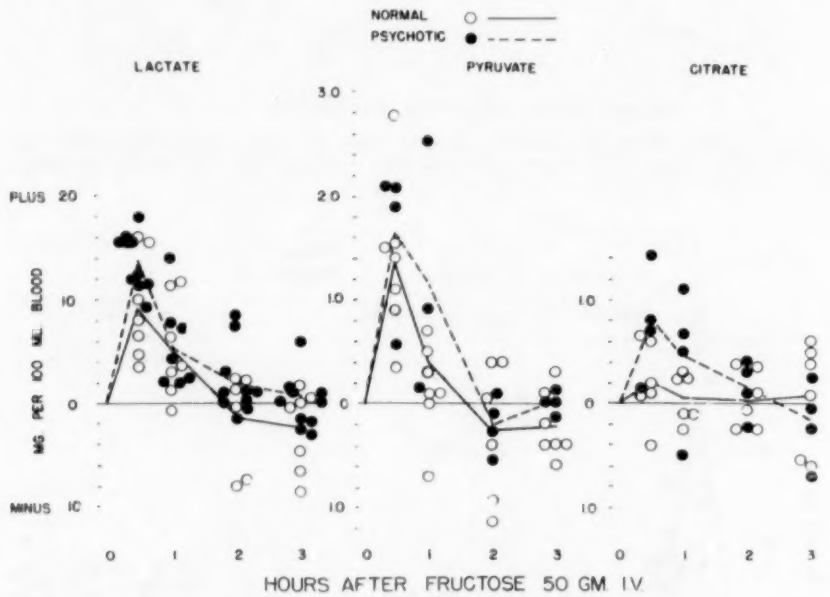

Fig. 7.—Effect of 50 gm. of fructose administered intravenously on concentrations of blood lactic, pyruvic, and citric acids. Open circles refer to normal subjects. Lines indicate average changes; broken line indicates changes in psychotic patients.

concentration also showed no significant differences between the two groups (Fig. 6). The normal subjects showed a greater average fall in serum inorganic phosphate concentration at the end of the 30-minute infusion, but thereafter both groups showed no change, or a slight rise (Fig. 6). Observations on the changes in blood lactic and pyruvic acid concentration showed small, questionably significant differences between the psychotic and the normal subjects (Fig. 7); the plasma citric acid concentrations rose in the psychotic patients, whereas the normal subjects showed no change (Fig. 7). There was much overlapping between the two groups, however. The changes observed when the fructose was given after treatment were not significantly different from those observed before treatment, except for a questionable difference in the serum inorganic phosphate curve (Figs. 8 and 9).

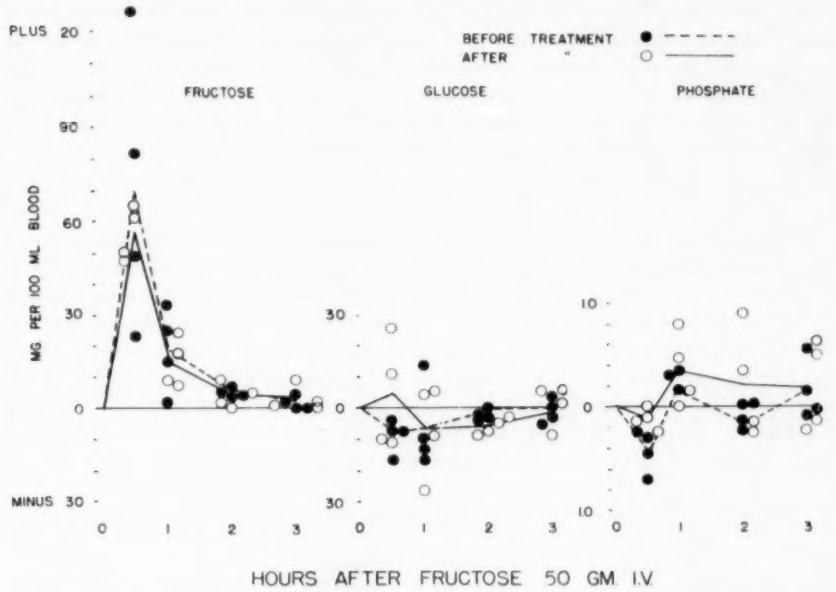

Fig. 8.—Effect of 50 gm. of fructose administered intravenously on concentrations of blood fructose, glucose, and phosphate in four psychotic patients before and after treatment. Open circles refer to changes after treatment. Lines indicate average changes; broken line indicates changes after treatment.

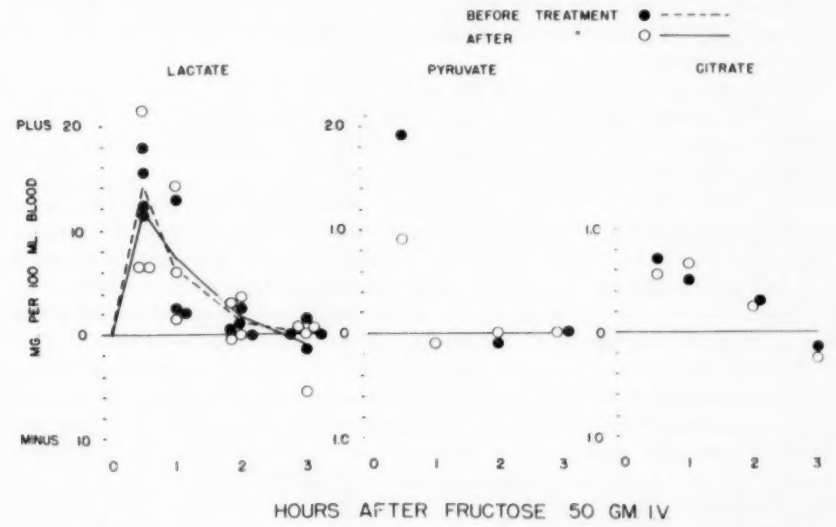

Fig. 9.—Effect of 50 gm. of fructose administered intravenously on concentrations of blood lactic, pyruvic, and citric acids in psychotic patients before and after treatment. Open circles refer to changes after treatment. Lines indicate average changes; broken line indicates changes in psychotic patients.

C. *Urinary Excretion of Phosphate, Lactate, and Citrate After Orally and Intravenously Administered Fructose.*—The changes observed in the urinary excretion of inorganic phosphate and of citric and lactic acids after orally and intravenously administered fructose were the same in the two groups. Five to 10% of the fructose infused intravenously was excreted in the urine in both groups over a three-hour period after the start of the infusion (Table).

COMMENT

Observations of fructose tolerance and metabolism in normal subjects made here are the same as those reported in the literature,* with two exceptions. First, the fructose blood concentration after the administration of 50 and 100 gm. of fructose by mouth did not return to the fasting level at the end of two hours, and, second, the serum inorganic phosphate rose between 0.1 and 0.55 mg. per 100 cc. above the fasting level one hour after both oral and intravenous administration of fructose; such an elevation above the fasting level has been considered abnormal by some other investigators.[17] The decrease in urinary inorganic phosphate excretion after levulose administration has been noted before, the first report being that of

Change in Hourly Excretion Rates After Administration of Fifty Grams of Fructose

Test	No. of Studies	Phosphate	Citrate	Lactate
Oral administration	9 psychotic 2 normal	— 4 to —36 mg.	+ 3 to +34 mg.	+ 1 to + 33 mg.
Intravenous administration	7 psychotic 2 normal	+10 to +44 mg.	+12 to +48 mg.	+93 to +327 mg.

Barrenscheen.[18] The excretion of large amounts of lactic acid and citric acid observed here after intravenous infusions of fructose represents a large metabolic loss to the organism.

The psychotic patients showed the same changes in blood fructose concentration as did normal subjects after oral or intravenous administration of fructose; i. e., the fructose entered the circulation and left it at a normal rate. However, the subsequent fate of the fructose was not entirely normal.

The administration of fructose by mouth to psychotic patients caused an abnormal rise in the blood glucose concentration after one-half to one hour. This abnormality is not specific for the psychoses discussed here; it has been observed in von Gierke's disease and in diabetes mellitus.† As in these other conditions, the abnormal rise undoubtedly is due to the initial normal conversion of some fructose to glucose by the intestine‡ and the subsequent sluggish utilization of this glucose.[1] In view of the finding of normal changes of blood fructose concentration in the psychotic patients after both oral and intravenous administration of fructose, it must be concluded that most of the administered fructose probably is largely and normally converted to glycogen[23]; however, a small portion of the fructose is metabolized to intermediate substances, some of which ultimately enter the tricarboxylic acid cycle.§ Following the administration of glucose in the psychotic

* References 7 through 17.
† References 9 through 11, and 19.
‡ References 20 through 22.
§ References 24 and 25.

patients there is often an excessive rise in blood lactic acid, and usually a rise, rather than the normal fall, in citric acid concentrations. The rise in plasma citric acid concentration observed here after the administration of fructose orally or intravenously to psychotic patients is probably explained by the formation of glucose from fructose in the intestinal wall and by the accumulation of breakdown products of fructose metabolism. These same considerations perhaps also explain the suggestive, but not significant, increased elevation in lactic acid observed in the psychotic patients.

The findings of the present study that no fructose intolerance was present rule out any commonly recognized type of hepatic disease as the cause of the abnormal carbohydrate metabolism of psychotic patients reported previously.[1]

SUMMARY

Pure fructose was administered to normal subjects and psychotic patients. Fructose tolerance was normal in patients with schizophrenic, manic-depressive, and involutional psychoses. The intermediate metabolism of the fructose was only slightly abnormal in the psychotic group. The most important difference from the normal was the occurrence of a rise, rather than the normal fall, in true blood glucose concentration after fructose given orally; this rise, together with the entrance of some fructose into the common metabolic pool, perhaps explains the moderately increased accumulation of citric acid in the blood of the psychotic patients who received fructose. This increased accumulation of citric acid was also observed after the intravenous infusion of fructose.

The finding of normal fructose tolerances in patients with the psychoses discussed here rules out any commonly recognized hepatic disease as the cause of the disordered intermediary carbohydrate metabolism described previously.[1]

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SERIAL ELECTROENCEPHALOGRAPHIC AND CLINICAL STUDIES IN A CASE OF PROLONGED INSULIN COMA

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PROLONGED coma is one of the important complications of insulin shock treatment for schizophrenia. With a normal or elevated blood sugar, induced by administration of dextrose, the patient remains comatose. Temperature becomes elevated, pulse becomes rapid, and there is a shifting neurological picture. Coma may persist from a few hours to several days, and when consciousness is recovered, there are frequently disturbances in the sensorium, memory changes, and other mental alterations of an organic type. The etiology is not clearly understood.[1]

Cases of prolonged coma obviously provide an excellent opportunity to study the brain potential correlates of reversible neurological and mental changes, usually severer and of longer duration than any which may be induced in humans by deliberate experimental manipulation. Since prolonged coma may occur in one-sixth of all patients subjected to a course of insulin coma therapy,[2] it is surprising that few EEG studies have so far been reported. The most extensive series are described in the recent papers of Yeager, Simon, Margolis, and Burch [3] on 12 cases and of Revitch [4] on 5 cases. Single cases have been reported by Proctor and Easton,[5] Goldfarb, Laughlin, and Kiene,[6] and Fister.[7] The findings of these authors have been relatively uniform. Diffuse slowing of rhythms was found associated with altered sensorium or organic confusion, and the EEG returned to normal as clinical recovery took place. There seemed to be a correlation of length of coma, degree of organic confusion, remission of mental symptoms, and degree of EEG abnormality.

EEG changes accompanying neurological complications of insulin have been described by Allan and Crommelin [8] in a juvenile diabetic and by Halle and Ross [9] in four cases undergoing coma therapy. The latter found localized EEG abnormalities, related to the neurological signs, which disappeared when the signs cleared up. Wyke [10] reported detailed serial studies, correlating clinical, EEG, and blood sugar observations, on a 9-year-old girl with hypoglycemia due to islet cell tumor of the pancreas. Wyke considered that the frequency spectrum of the EEG bore a more direct relation to the clinical picture than did the blood sugar level.

The present paper is a report, with serial EEG studies, of a particularly interesting case of prolonged coma. Most of the important cerebral complications following coma were observed in this case, and it was possible to correlate state of consciousness with EEG changes.

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CLINICAL OBSERVATIONS

The patient, a 36-year-old white married woman, was admitted to the Allan Memorial Institute of Psychiatry for the third time on July 6, 1953. The first episode of overt psychosis had occurred in 1949. Since that time she had been receiving psychiatric treatment, including E. C. T., somnolent insulin therapy, and intensive psychotherapy, almost continuously at one of three hospitals. Previous attempts to administer a regular course of insulin coma had been abandoned because of delayed reactions and pulmonary complications.

From the age of 17 the patient had felt that she was different from other people and that people made disparaging remarks about her. During some acutely psychotic episodes she had appeared severely depressed. At other times her symptoms included the delusion that she emitted unpleasant odors, withdrawal, apathy, inappropriate laughter and tears, uncontrollable erotic feelings, muscular aches and pains, hyperhidrosis, and phobias of being alone and traveling on streetcars. Prior to the last admission the chief symptoms were ideas of reference, the belief that she smelled, and auditory hallucinations in the form of children's voices shouting that she smelled. She also had some washing rituals. The diagnosis was consistently paranoid schizophrenia.

The last readmission took place because the referring psychiatrist felt that a serious attempt should be made to give the patient a full course of insulin coma therapy. Treatment was started on July 13. By Sept. 10 a total of 41 treatments, with a cumulative total of 16¼ hours of coma, had been administered. For the 42d treatment, on Sept. 11, the dose of insulin was 375 units. Coma was noted at 9:15 a. m. At 10:15 a. m. 500 cc. of 30% dextrose was given by gavage, and at 11:00 a. m. 200 cc. of 20% dextrose was given intravenously. When there was still no response, treatment for prolonged coma was instituted.

Prolonged coma probably lasted about nine hours, i. e., until 6:00 p. m. For at least the last three hours the patient was hyperglycemic. Blood sugars were 50, 127, 225, and 280 mg. per 100 cc. at 2:00, 3:00, 4:00, and 8:00 p. m., respectively. Elevation of the blood sugar was achieved by a total dextrose administration, on Sept. 11, of 200 gm. by vein and about 900 gm. orally, mainly by gavage. Additional supportive measures employed were nikethamide (Coramine), epinephrine (Adrenalin), vitamin B complex, interstitial isotonic saline (with hyaluronidase), and penicillin.

At 6:00 p. m. the patient seemed aware of verbal stimuli and was less restless. At 7:00 p. m. her eyes appeared to be focusing, but she did not reply to questioning. At 10:00 p. m. she sat up in a chair, walked around the room a few times with a very unsteady gait, smiled, nodded, and shook her head, but did not speak. At 9:00 a. m., on Sept. 12, the patient was able to answer when spoken to. At 10:00 p. m. she seemed to be concerned about the appearance of her hair and talked more than previously, but with considerable effort and mumbling speech.

On Sept. 13 the patient was awake but had to be persuaded to engage in any routine activity. She complained of dizziness and fatigue. She displayed erotic behavior, attempting to embrace and kiss any man approaching her. She was somewhat disoriented as to time, believing that it was one year later and being unable to tell the day. She knew that she was in the Allan Memorial Institute but could not find her room. She did not remember the names of her present or previous physicians.

On neurological examination it was observed that she had a shuffling gait. The cranial nerves were normal. Upper limbs showed very slight spasticity. All reflexes were exaggerated but equal. The lower limbs showed a general weakness of all muscle groups, also slight spasticity. Plantar reflexes were flexor. Abdominal skin reflexes were equal and present.

For the next several days the nursing notes repeatedly stated that the patient appeared dazed. She required help in walking. She would sit in a chair and fall asleep very readily, appeared very vague when aroused, and became annoyed when questioned too frequently. She would not engage in any spontaneous activity, seemed to have no interest in her personal appearance, and did not socialize. A few times, when her husband visited her, she fell asleep in his presence.

Examination, on Sept. 15, revealed that the patient was able to follow simple commands but was unable to execute compound ones, such as "Touch your nose with your left thumb." She recalled six digits forward, but did not remember an address given to her five minutes previously. She named a bed, a watch, her right thumb, and a drawer in a chest of drawers, but she could

not name a chest of drawers. The examiner's impression was that she was mildly disoriented, that she had some impairment of memory for recent events, that her concentration was poor, and that there was evidence of a minimal nominal aphasia.

During the next few days the nurses began to note behavior in relation to imaginary objects. She asked a nurse to comb her hair and handed the nurse an imaginary comb and imaginary hairpins. She appeared to light and smoke imaginary cigarettes frequently.

On Sept. 19 examination revealed no improvement in orientation, recent memory, or ability to concentrate. When the patient was asked to do the Serial 7 test, she laid her head on the desk and went to sleep. She was unable to give the days of the week backward. She performed simple calculations fairly well, but displayed perseveration in such responses as "ten 10's are 10 and there are 25 25's in 100." Speech seemed normal.

On Sept. 21 the patient seemed to be dragging her right foot when walking. On Sept. 23 she appeared somewhat less drowsy and was able to cooperate longer in the mental examination. She still appeared perplexed, and disorientation for time and impairment of recent memory persisted. A tendency to confabulation was noted; e. g., the patient said that she was glad she was going to a resort for the week end (untrue), and when asked when she had last been there, said, "Last week end."

During the next several days the patient displayed negativistic behavior and continued to appear as though she were lighting and smoking imaginary cigarettes. On Sept. 30 a complete neurological examination was essentially negative. She complained spontaneously about difficulties in memory that day, and, on Oct. 1, she cried over lack of memory and had to be reassured.

On the afternoon of Oct. 1 the patient reported that while walking with the ward group, at 3:30 p. m. exactly, she suddenly felt a great change take place in her. She stated that she suddenly woke, and that previously she had been in a kind of haze. The change was described as a pleasant and wonderful feeling, as though she had at last found herself. The last events which she remembered clearly had taken place prior to her prolonged coma, although she had a vague memory for the occurrences of the past few days. She reported that prior to regaining full contact she heard people vaguely, as though she were far away from them. Now they were closer. She discovered her untidy appearance and was shocked. Her cheerful mood was thought to be appropriate, rather than euphoric. That night she attended the dance and socialized well. The next day she was well dressed, made up, and behaved in a spontaneous fashion.

On Oct. 3 the patient went out for a social evening with her husband. She was not afraid, enjoyed herself, and voluntarily decided to meet some neighbors whom she had previously feared to encounter, having felt that they didn't like her.

On Oct. 4 her ideas of reference seemed to be gone, and it was felt that most of her schizophrenic symptomatology had disappeared. She still admitted to some feelings of unreality, but said they were less than they had been three days before. In these feelings, everything seemed strange, pictures in a magazine seemed odd, and her voice seemed far away. Orientation was now correct, and she showed excellent attention. No flaws could be found in the amnesia for the period from Sept. 11 to Sept. 30. She could not be made to confabulate. Her number sense was greatly improved. Serial 7 Tests were carried out, with one or two errors. Speech was normal, and she named objects correctly.

She continued to progress favorably and was discharged from full-time hospital care on Oct. 14. She continued to attend for thrice-weekly somnolent insulin treatments and weekly interviews.

Since her discharge marked clinical improvement has persisted. Delusions, obsessions, and phobias have been absent. She has been more outgoing, and the marital relationship has improved.

ELECTROENCEPHALOGRAPHIC OBSERVATIONS

Seven examinations were carried out on this patient, the first in December, 1951, the second in July, 1953, and the remaining five following the prolonged coma. The last test was done on Nov. 26, some six weeks after discharge from hospital. Records were taken on Grass instruments with Bentonite paste electrodes. In one exami-

nation, the third postcoma one, nasopharyngeal electrodes were inserted. In all tests hyperventilation for 3.5 minutes was carried out. Intermittent photic stimulation was done in the last six tests.

The first two EEG's, 18 months apart, were essentially similar, with mean alpha frequency about 10 cps and a rather wide spread of frequencies. There were no significant abnormalities at rest, with hyperventilation, or in response to photic stimulation (Fig. 1*A*). Photic driving was optimal at 10 cps.

The first postcoma EEG was obtained six days after the onset of prolonged coma (Fig. 1*B*). The two outstanding features were (1) general slowing of alpha frequency below 8 cps, and (2) diffuse slow wave activity, ranging from 2 to 6 cps,

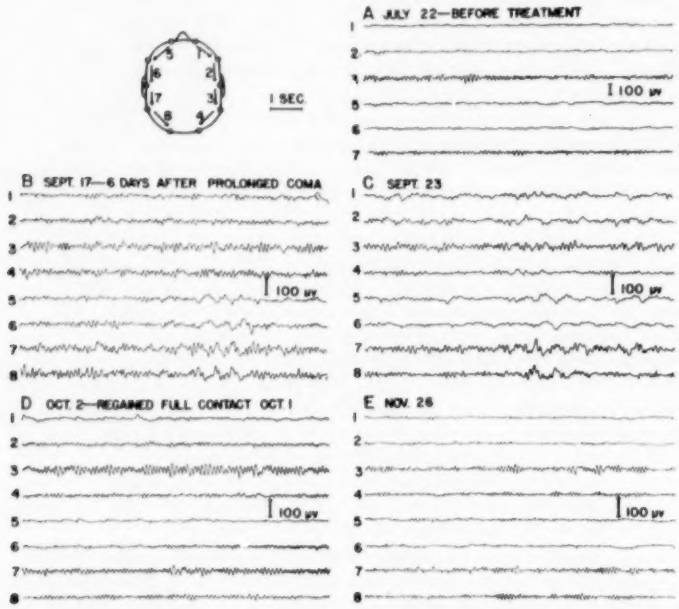

Fig. 1.—Serial EEG tracings on five occasions. Note appearance of diffuse slow waves and left temporal slow wave focus after prolonged coma (*B*). Note disappearance of slow waves after recovery of contact (*D*).

which appeared maximal in the left temporal area and which was also seen occasionally in the right temporal area. The slow activity was augmented slightly by overbreathing and was diminished when the patient's attention was stimulated by opening of the eyes or ringing of the telephone. The largest-voltage slow waves showed phase reversals primarily in the left temporal area. In response to photic stimulation there was practically no driving.

The second postcoma EEG, on Sept. 23, was very similar to the previous one. There seemed to be some diminution of voltage, a slight increase in alpha frequency, and a smaller amount of slow wave activity (Fig. 1*C*). Photic stimulation did not produce any noticeable driving. The slow wave abnormality from the left temporal electrodes was once again clearly demonstrated.

The third postcoma EEG (Fig. 1*D*) was taken on Oct. 2, the day after the patient appeared to regain full contact with her environment. There was a marked improvement over the previous tracing. Alpha frequency was somewhat increased; slow wave activity was minimal, and the slow wave abnormality in the left temporal area was demonstrated only with widely spaced electrodes and in response to overbreathing. No abnormalities were recorded from the nasopharyngeal electrodes. Photic stimulation produced some driving at both 10 and 15 cps.

The next EEG was obtained on Oct. 13. It showed an increase of alpha frequency to about 10 cps, and the only abnormality was a slight amount of slow wave activity localized in the left temporal area and brought out clearly by hyperventilation. There was some photic driving, but this was rather slight.

The final tracing was done on Nov. 26, six weeks after the patient's discharge (Fig. 1*E*). Alpha frequency was normal. Careful inspection of the record still

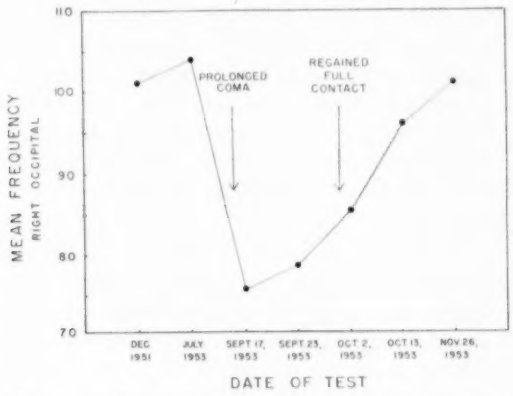

Fig. 2.—Mean right occipital frequencies. Note gradual increase to pretreatment level.

showed a small amount of slow wave activity localized in the left temporal area, but this was minimal. Photic stimulation produced good driving, particularly at 10 cps.

Figure 2 shows the relationship between background frequency and the patient's changing state of awareness. The mean frequencies plotted in the graph were derived by a method similar to that of Romano and Engel.[11] The frequency of all waves occurring at 13 cps or less was determined in 30 consecutive seconds of tracing from the right occipital to the right ear derivation. During the period of impaired consciousness the patient's alpha frequency was low. With improvement it increased, regaining the pretreatment level some 10 weeks after the onset of prolonged coma. It is to be noted that even though the patient experienced a dramatic change in level of consciousness on Oct. 1, the change in alpha frequency was not nearly so dramatic.

COMMENT

The complications of prolonged posthypoglycemic coma in this patient were an organic mental syndrome, lasting at least three weeks, together with transitory nominal aphasia and possible right-sided paresis. These clinical changes were reflected in

the EEG. Serial EEG study of such cases seems to provide a useful procedure for assessing and following the course of recovery from the complications of prolonged coma.

Spencer has reviewed the postmortem brain findings in deaths after prolonged coma. Usually, there was widespread neuronal damage, particularly in the cerebral and cerebellar cortex, accompanied by glial and vascular changes. The greatest vessel damage seemed to be in the endothelium, with proliferation of cells leading to narrowing, or even obliteration, of the lumen and secondary thrombus formation. There were also perivascular hemorrhages. These pathological findings suggest a number of possible mechanisms for production of reversible focal abnormalities in the EEG, such as the left temporal one in the present case. For example, small thrombi could occur, followed by edema and neuronal damage or destruction.

The patient's clinical course involved sudden and dramatic recovery of full contact with the environment, following which there was amnesia for the preceding three weeks. All available evidence suggests that this entire period was one of genuine organic confusion. In the EEG, recovery of contact was associated with sudden disappearance of gross slow wave activity. However, alpha frequency increased only in a gradual manner and took some weeks longer to reach the patient's normal level. These EEG data suggest a distinction between a state of grossly altered awareness, characterized by slow waves, and a state of apparently normal awareness, but with residual cerebral change still reflected physiologically in slowed alpha frequency.

This distinction may perhaps be related to different characteristics of the diffuse projection system at brain stem and thalamic levels. The ascending reticular activating system in the brain stem appears to play an important role in the maintenance of normal wakefulness.[12] Its action upon electrocortical activity seems to be generalized; i. e., stimulation of it affects the entire cortex. On the other hand, at the thalamic level the reticular system appears capable of regulating cortical activity in a more localized manner.[13] In a case of deep and prolonged unconsciousness it would seem reasonable to assume that the reticular system was damaged. The three-week period of impaired awareness following coma, associated with EEG slow waves, may be readily interpreted as resulting from residual damage at the midbrain level. Recovery could then occur at this level to an extent sufficient to allow an apparently normal state of awareness. This implies a "step-function," related to consciousness. However, there might still be sufficient residual change at the thalamic level to produce slowed alpha rhythm, which might recover in a gradual, rather than stepwise, fashion. Slowed alpha frequency is, by itself, not incompatible with well-maintained environmental contact. A patient with pituitary deficiency, recently studied in this laboratory, did not give evidence of altered awareness at any time, but his alpha rate increased from 7 to 9.5 cps with appropriate hormone therapy.

Clinical improvement after accidental prolonged coma has been observed since the early days of insulin therapy, but results have been highly variable. In Revitch's series,[4] those patients who sustained the most marked brain damage seemed to show the greatest remission of psychotic symptoms. The present case would fit this generalization. It is perhaps noteworthy that the patient lost not only her more grossly psychotic symptoms, but also her symptoms, such as phobias, that were neurotic in

character. Of some importance in this connection might have been the fact that, even though the illness was of several years' duration, the patient had never shown signs of personality deterioration.

SUMMARY

This paper describes clinical and EEG findings in a case of prolonged coma following insulin therapy for schizophrenia. EEG changes reflected the neurological and mental complications. An attempt is made to interpret these correlations with reference to the properties of midbrain and thalamic reticular systems.

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Prof. D. E. Cameron granted permission to publish this study on his patient, and Mrs. Julaine Martin gave technical assistance.

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ANALYSIS OF SOME FACTORS IN SPONTANEOUS SUBARACHNOID HEMORRHAGE

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THE TREATMENT of spontaneous subarachnoid hemorrhage is based on the reports in the literature of series of cases. There have been conclusions drawn from these series which at times have been conflicting. Certainly a very large series of cases followed in extreme detail and analyzed minutely would be of great help in resolving many of the controversies which have risen out of the inconsistencies reported in the literature. However, until this critical series is presented, it would be of value to consolidate these reports so that as much information as possible might be gained from the available data. This would also point up the factors that should be checked in future studies of this type.

In this presentation the major series of spontaneous subarachnoid bleeding * have been gathered together, and the material presented has been consolidated, wherever possible, so that a more informative result could be obtained.

The series used in this paper have been taken from clinical material in which the diagnosis of spontaneous subarachnoid hemorrhage was made from the syndrome of sudden onset of severe meningeal irritation, with or without focal neurological signs, with bloody or xanthochromic spinal fluid, and without indication of underlying conditions, such as blood dyscrasia, trauma, syphilis, infections, and neoplasms. The appellation, spontaneous subarachnoid hemorrhage, used for the cases under discussion, although not strictly accurate, pathologically has the virtue of grouping those cases * that have the common problem of diagnosis. The term has the additional value of common usage.

SURVIVAL

The most important question is that of survival. The total number of cases with subarachnoid hemorrhage surveyed was 1,490, and of these, 750 died (51% of all the cases with subarachnoid hemorrhage). However, in 388 cases the duration of follow-up of the cases is not listed. In the 1,102 cases (74% of the total) in which the follow-up was given, there were 591 deaths (54% of the cases in which a follow-up is listed). These cases were followed for an average of 7.8 years.

There were three series in which an especial effort had been made to obtain long-term results.† In these series a total of 578 cases were followed for an average of 8.6 years, and of these patients 57.2% died (331 patients). In two of these series, 77 were followed for 5 to 10 years, and of these patients 6 died (7.8% of those followed). In one series, 25 cases were followed for 10 to 33 years, and of these

* References 1 through 14.
† References 4, 6, and 13.

TABLE 1.—*Mortality Rate of Total Number of Patients, from Time of Onset of First Attack*

Survival Time from Onset of First Attack	Mortality Rate, in %, from Time of Onset of First Attack	Amount of Change, %
1 wk	27	..
2 wk	33	6
1 mo	38	5
3 mo	49	11
1 yr	53	4
5 yr	54	1
10 yr	57	3
30 yr	69	12

TABLE 2.—*Mortality Rate, in Percentages, Due to the First Attack in Patients with Subarachnoid Hemorrhage, per Designated Week*

Survival Time, Wk.	Deaths Due to First Attack in Designated Week, %
1	25.6
2	1.1
3	0.7
4	0.4

TABLE 3.—*Percentage of Total Patients with Subarachnoid Hemorrhage That Died in the Designated Week of a Recurrent Attack*

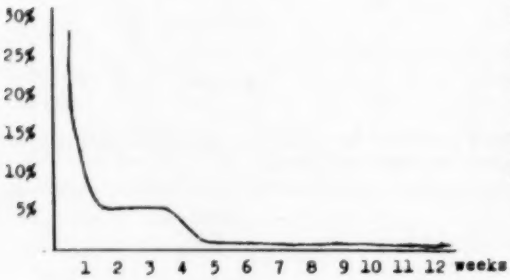
Survival Time, Wk.	% of Deaths
1	1.8
2	5.1
3	2.9
4	1.7

TABLE 4.—*Incidence of Recurrence as Cause of Death in Cases of Subarachnoid Hemorrhage*

Time of Death	Total No. of Cases in Which Recurrences Are Considered (Cr)	Recurrences, No.	Deaths Due to Recurrence (Dr)	Per Cent of Deaths in Total No. of Cases in Which Recurrences Were Considered (100·Dr/Cr)
Within 2 wk	406	44	28	7
2 to 3 wk	184	14	10	5
3 to 4 wk	184	9	7	4
1 to 2 mo	184	12	4	2

patients 3 died (12% of the cases followed for 10 to 33 years). These figures indicate that after 33 years approximately 70% of the total cases will be dead because of subarachnoid hemorrhage.

Of prime importance in any consideration in the prognosis of subarachnoid hemorrhage is the incidence of recurrence which is the cause of death after the first three months. Examination of the curve in Figure 3 shows that the curve of total deaths is made up of two distinct components. There is a lower peak over the period of a month due to the deaths from recurrences, and a second peak, with



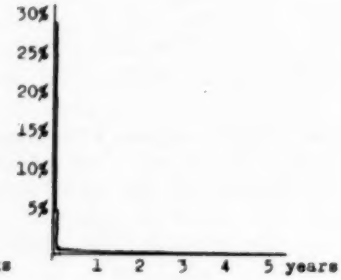
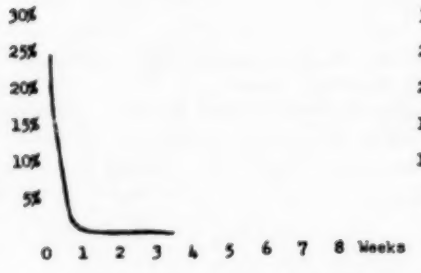


Fig. 1 (left).—Percentage of cases of death due to spontaneous subarachnoid hemorrhage, plotted against length of time from onset to three months after the onset, in each week.

Fig. 2 (right).—Percentage of deaths due to spontaneous subarachnoid hemorrhage, plotted against time, in each year.



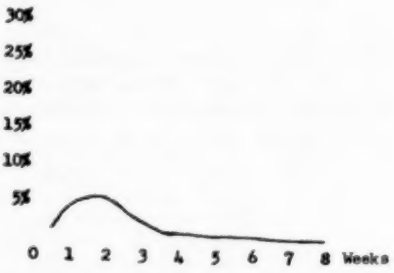


Fig. 3 (left).—Deaths due to the first attack occurring in each week, in percentage of total cases with spontaneous subarachnoid hemorrhage, plotted against length of time from onset.

Fig. 4 (right).—Deaths occurring in each week due to recurrence of the subarachnoid hemorrhage, in percentage of total cases with spontaneous subarachnoid hemorrhage, plotted against length of time from onset.

a very high level, in the first week, which represents the mortality in the first attack. This peak falls very rapidly, almost to the base line by the middle of the second week, and to the base line by the fourth week. There continues to be deaths due to recurrences at a fairly steady rate.

These deaths occurred at the rate of 1% a year from the end of the 1st to the 5th year, and then at the rate of 0.6% a year for the next 20 years, which is as long as there was follow-up in any series in the literature. It would seem from the way

the curve trails out that a person with subarachnoid hemorrhage would eventually die of a recurrence if he should live long enough; however, by this mode of calculation the last patient would die 80 years after the initial attack.

PROGNOSTIC VALUE OF SIGNS

Another facet of the problem of spontaneous subarachnoid hemorrhage that could be considered with value in this study is the prognostic significance of the common signs of bleeding. In 141 cases coma was reported. This figure was 41% of the total cases (345) of the series in which the incidence was recorded. Of the cases with coma, 91 died. This figure is 65% of the cases that had coma, and 26% of all the cases in the series that reported on the presence of coma.

TABLE 5.—*Prognostic Significance of the Common Signs of Bleeding*

Sign	Total No. of Cases in Which Sign Was Reported on Cs	Cases with Sign S	Cases with Sign That Died Sd	% of Cases with Sign That Died 100·Sd/s	% of Total Cases with Sign Reported on That Died 100·Sd/Cs
Coma *	345	141	91	65%	26%
Convulsions *	345	41	27	66%	8%
Hypertension †	386	94	52	55%	14%
Papilledema ‡	215	16	6	38%	3%

* References 3, 5, 6, and 7.
† References 5 through 8.
‡ References 3, 5, and 7.

TABLE 6.—*Influence of Age on Survival*

Age, Yr.	% of Total Cases, by Age	% of Deaths, by Age	Probability [15]
Under 21	4	3	....
21 to 30	9	17	0.57
31 to 40	19	17	....
41 to 50	26	11	0.48
51 to 60	25	31	....
61 to 70	11	17	....
Over 70	7	3	....

The other signs of subarachnoid hemorrhage were not reported in the literature in sufficient detail to admit analysis.

It would seem that an avenue of probable important observations would be in assessing the mortality in combinations of symptoms. A reasonable expectation would be that in cases with both coma and convulsions there would be a very high mortality, and this could also be expected with coma and hypertension. This finding would be important in determining treatment, for when a conservative course is almost universally fatal a more radical procedure is indicated.

INFLUENCE OF AGE ON SURVIVAL

A set of series with a total of 453 cases showed ages of the cases, at the onset of the bleeding. While in another set of series, totaling 65 cases, the ages were indicated of the patients that died. In this last set, there were 35 deaths, which

figure is 54% of the total cases under consideration. This mortality indicates that this series is representative of the group of series as a whole, for this mortality rate is almost identical with that of the entire group.

Statistical analysis of the two groups with the greatest difference shows that the probability of their coming from the same universe is so high that one can assume that they do. This analysis indicates that the age of onset is not a factor in the production of a fatal termination.

Magee's ‡ series is considered separately because it deals with veterans of World War I and thus deals with a restricted group agewise. However, comparison of the occurrence by age and death by age gives support to the thesis that age is not a factor in the production of death.

INCIDENCE OF DISABILITY

These patients not only die of the hemorrhage but are also maimed. Series which reported on the incidence of significant residuals, such as hemiplegia, aphasia, monoplegia, defects in mentation, personality difficulties, and neurotic manifestations to the point of disability, etc., totaled 990 cases of spontaneous sub-

TABLE 7.—*Influence of Age on Survival, in Veterans of World War I*

Age, Yr.	Cases	Deaths	Cases, % of Total Cases	Deaths, % of Total Deaths
Under 20	9	5	6	6
21 to 30	76	37	50	44
31 to 40	56	37	37	44
41 to 50	9	5	6	6

arachnoid hemorrhage. A total of 93 patients were severely to moderately damaged. This figure is 9.4% of all patients with subarachnoid hemorrhage. In consideration of the results of the bleeding, the number of people maimed should be kept in mind, as well as the number of those who die.

INCIDENCE OF ANEURYSMS

In the literature there are 11 series, with a total of 521 cases of spontaneous subarachnoid hemorrhage, in which either autopsy or angiography was done. A series was used if it did not contain subarachnoid hemorrhage due to neoplasm, syphilis, trauma, blood dyscrasia, or infection. However, if a series did contain such cases, it was used if it was well enough noted that they could be eliminated from the calculations.

A total of 212 of the 521 cases with hemorrhage were found to have aneurysms, which figure is 38.6% of the cases examined. Unfortunately, there is a large scatter in the series, making one somewhat dubious of complete acceptance of the average as the correct incidence of this condition in nature. As can be noted in Table 8, the percentages range from 9.7% to 80%. The groups that were compiled earlier are the smaller ones, indicating that possibly when there was less interest in the condition, a less exacting search was made for the aneurysm. This would tend to

‡ Reference 3.

reduce the reported incidence of aneurysm. The average of the series in which angiography was used as the mode of diagnosis was much higher, being 66.4%. It is difficult to place a great deal of validity on this figure, for it is the result of only three series, two of which are rather small. However, from inspection of the figures, one could logically assume that this percentage is closer to the true one than the value of 38.6% and that the true figure lies between the two.

TABLE 8.—*Incidence of Aneurysms in Cases with Subarachnoid Hemorrhage*

Author	Cases of Subarachnoid Hemorrhage C	Mode of Diagnosis	Cases of Aneurysm A	% of Cases with Subarachnoid Hemorrhage That Had Aneurysms 100·A/C
Wolf, Goodell, and Wolff [1]	8	Angiography	3	37.5
Dekaban and McEachern [10]	9	Angiography	4	44.4
Strauss, Globus, and Ginsburg [7]	11	Autopsy	5	45.4
Hyland [8]	55	Autopsy	44	80.0
Dekaban and McEachern [10]	33	Autopsy	26	78.8
Ohler and Hurwitz [5]	5	Autopsy	0	0.0
Symonds [17]	64	Autopsy	11	9.7
Sands [9]	106	Autopsy	15	23.3
Falconer [4]	69	Angiography	50	72.5
Courville [18]	114	Autopsy	16	14.0
Total	521	.....	212	38.6

[4] Falconer, M. A., in discussion on Norlen, G., and Falconer, M. A.[14]

TABLE 9.—*Incidence of Multiple Aneurysms in Total Cases with Aneurysms*

Author	Cases with Aneurysms C	Cases with Multiple Aneurysms M	% of Cases with Aneurysms That Had Multiple Aneurysms 100·C/M
Dandy [2]	108	16	14.8
Magee [3]	43	4	9.3
Wolf, Goodell, and Wolff [1]	3	0	0.0
Hamby [6]	44	2	4.5
Dekaban and McEachern [10]	38	10	26.3
Strauss, Globus, and Ginsburg [7]	5	1	20.6
Ask-Upmark and Ingvar [13]	28	1	3.6
Total	263	34	12.9

MULTIPLE ANEURYSMS

There is, fortunately, a clearer picture when the multiplicity of aneurysms in a single patient is concerned. There are seven sets in the literature which correspond very well with each other and with the average of the total. Of 263 cases with aneurysm, 34 had multiple aneurysms, which is 12.9% of the total. Therefore, one could safely assume that this figure is a good approximation of the true incidence in nature.

McDonald and Korb [16] in their review of 1,125 cases in the literature, found only 7 cases in which more than one aneurysm was found. This figure is 0.62% of the total and is out of line with the recent reports. The McDonald and Korb cases were taken from the earlier literature, so these were not included in the averaging.

OTHER CASES OF BLEEDING

In all of the reports, when an aneurysm was not found, no cause of bleeding was found, except for the very occasional appearance of an angiomatous malformation. In 154 cases of subarachnoid hemorrhage, only 3 such malformations were found, approximately 2% of the group investigated.

The presence of a large group of hemorrhage in which no cause was found at autopsy would suggest that there may be some microscopic defect present, such as the malformation of blood vessels, one of the causes of intracerebral hematoma.[19]

COMMENT

Spontaneous subarachnoid hemorrhage is a malignant disease, with the incidence of death a factor of the length of time from the onset of the first hemorrhage. The mortality rate is generally assumed to be between 40% and 50%, a figure which is valid only for the period from one month to one year. Before one month the mortality rate is lower, and after one year it is greater. This additional dimension is of importance in formulation of the therapeutic program.

The mortality of subarachnoid hemorrhage falls into two categories: those cases in which death is due to the first attack, and those in which the patient succumbs to a subsequent bleeding. A great deal of attention has been given to the group with subsequent bleeding, and many of these people can be helped with definitive treatment. The physician is able to offer nothing except palliative and supportive treatment to those who die in the first attack, which group represents approximately 28% of all cases with subarachnoid hemorrhage.

Only four of the signs found in this condition are reported in the literature in sufficient detail to be analyzed for their prognostic significance. These signs are coma, convulsions, hypertension, and papilledema. The appearance of any of the first three signs, singly, the first two to a greater degree than the third, is indicative of a poor prognosis for life. There are no data on the prognosis when a combination of these four signs exists, but one could logically assume that this would be an even more direful portent.

A consideration of the relation of the age of the patient at the onset of the hemorrhage shows that age has no effect on the mortality rate.

Approximately 10% of all patients with subarachnoid hemorrhage are maimed to a significant degree, in addition to those patients who die. This fact also should be considered in any thought on the prognosis of subarachnoid hemorrhage.

It is not clear from the literature just how often there is an aneurysm when there is subarachnoid hemorrhage. The best inference is that it occurs in the neighborhood of 50%. This incidence is an important consideration from the point of view of surgery, for only the cases with demonstrable aneurysms, arteriovenous malformations, and tumors can be treated surgically, and not all of these cases can be so treated. Certainly the presence of such a large group in which the cause of bleeding is not found is an academic and clinical problem of great magnitude.

A frequent contraindication to surgery is multiplicity of the aneurysm, which is present in about 13% of all patients that have aneurysms. This finding shows that a thorough angiographic study is indicated before surgical treatment is done.

Angiomatous malformation was found to be an uncommon cause of spontaneous subarachnoid bleeding.

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USE OF N-METHYL-α,α-METHYLPHENYLSUCCINIMIDE IN TREATMENT OF PETIT MAL EPILEPSY

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FOR SEVERAL years we have been searching for new and more efficient petit mal drugs to supplement the dearth of standard drugs already available to the medical public. We have tested a number of different chemical groups, but to date that group of chemical compounds known as the succinimides appears to offer the most promise. It has been our opinion, too, developing out of our clinical experience, that it is futile to hope to find one drug which will be the touchstone of effectiveness in all cases of petit mal epilepsy. The armamentarium of petit mal medication is badly in need of drugs other than phenobarbital or trimethadione (Tridione), regardless of how effective these drugs may be, since it is common knowledge that whereas one drug may not be beneficial in a particular case, another may be highly effective.

While petit mal seizures are not so dramatic as those of the grand mal type, they may be equally devastating in their effect upon the development of the child's personality. This effect on the personality, in our experience, is much more important than the seizures themselves, but regardless of any form of psychotherapy used the results are poor unless the seizures can be reasonably well controlled. It is difficult enough to teach an adult to accept a disability, and the problem is even greater in a child, since all too frequently other children will not let him forget his disability.

In conformity with this experience, we introduced one succinimide (N-methyl-α-phenylsuccinimide; Milontin; PM 334) which has relatively low toxicity to date and good anti-petit-mal action. Subsequent reports by Smith and Forster [1] and Millichap [2] indicate that our findings were substantially correct.

This presentation is concerned with our findings on still another succinimide compound, N-methyl-α,α-methylphenylsuccinimide, which has a high degree of effectiveness, especially in the treatment of intractable cases, is prompter and more dramatic in its action, and, furthermore, appears to have some degree of effect in controlling attacks of the so-called psychomotor type, which are noted for their resistance to all known forms of therapy. The effective dose is relatively small. It is, however, more toxic than PM 334, but not disturbingly so, and these side-reactions are more than counterbalanced by the effectiveness of the drug.

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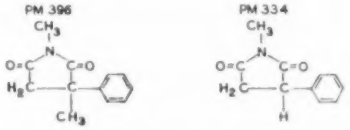
PHARMACOLOGY

N-methyl-α,α-methylphenylsuccinimide, hereinafter designated by its laboratory number, PM 396, for the sake of brevity, was synthesized in the laboratories of Parke, Davis & Company. A comparison of the respective molecules of PM 396 and PM 334 reveals that these drugs are identical except for the additional weight of a methyl group substituted for hydrogen in the number 3 position of the heterocyclic compound (Figure).



In the animal laboratory,* a dose of 65 mg. of PM 396 per kilogram of body weight was effective in protecting rats against convulsions induced by pentylenetetrazol (Metrazol), as against a dose of 125 mg. of PM 334 and a dose of 500 mg. of trimethadione per kilogram, suggesting an effectiveness, gram for gram, roughly of twice that of PM 334 and of eight times that of trimethadione. Biochemical, hematologic, and urinary findings remained within the normal range in animals given relatively large doses for prolonged periods of time.

CLASSIFICATION OF ATTACKS

In this study the same classification of petit mal epilepsy is used as that reported in the investigation of other experimental drugs,† i. e., a purely empirical classification based upon direct clinical observation, as given below:

1. Pure petit mal (pyknolepsy)—manifested by transient loss of consciousness only, without loss of postural tone or the presence of concomitant motor phenomena

2. Mixed petit mal—that form of epilepsy which manifests itself predominantly in transient loss of consciousness and minor motor phenomena, such as clonic movements of the upper extremities

3. Petit mal combined with other types of seizures

MATERIALS AND METHODS

This preliminary report on PM 396 is based on a study of 54 patients previously treated over a long period of time with various drugs. The number of attacks was reported on a daily calendar sheet by each patient and, in turn, recorded on a duplicate sheet for statistical analysis and permanent record.

It has been our experience that regardless of the type of medication given the majority of the patients seem to improve if treatment is carried on over a period of years. It is therefore necessary to define the nature of the base line used in judging the relative effectiveness of medication and to revise this base line from time to time.

One method which we used for the evaluation of petit mal medication was to record the anticonvulsant activity of the drug administered immediately preceding PM 396 as a base line for judging the effectiveness of PM 396, thereby showing its superiority or inferiority to previous medication.

We also studied the effect of PM 396 on patients who had been given a placebo for several weeks before initiation of drug therapy. Thirty-six patients were so treated.

* Studies by Dr. Graham Chen, Parke, Davis & Company Laboratories.

† References 3 and 4.

The risk entailed in the discontinuance of drug therapy in petit mal, is, of course, not nearly so great as that in grand mal epilepsy, in which there is danger of the patient going into status epilepticus. Additional information is also provided as to the effect upon seizures when medication is discontinued after a series of effective drugs has been given.

Data reported in the accompanying Tables are presented with the two base lines described above as criteria for judging the degree of seizure control with PM 396.

We believe, however, that we should call attention to the fact that in using as a base line the drug given immediately preceding PM 396 to estimate the effectiveness of PM 396, we penalized our data heavily by eliminating all patients who had been completely controlled by other drugs for a period of four consecutive weeks, or those on the preceding drug. In this way, of course, we favored the more intractable patients who had shown relatively little response to any previ-

TABLE 1.—*Effectiveness of PM 396, Using Base Line Derived from Experimental Drug Administered Immediately Preceding PM 396*

No. of cases	54
Average no. of seizures per week on previous medication	49
Average no. of seizures per week on PM 396	43
Reduction in seizures	12%
Average daily dose, gm	1.1
Average duration of treatment, wk	13
Complete control	22%
Practical control (80 to 99%)	9%
Partial control (5 to 79%)	29%
No effect (0 to 4%)	24%
Condition worse	16%
Toxic signs	29%

TABLE 2.—*Effectiveness of PM 396, Using a Placebo Base Line*

No. of cases	26
Average no. of seizures per week on placebo	108
Average no. of seizures per week on PM 396	48
Reduction in seizures	56%
Average daily dose, gm	1.1
Average duration of treatment, wk	4
Complete control	17%
Practical control (80 to 99%)	17%
Partial control (5 to 79%)	30%
No effect (0 to 4%)	8%
Condition worse	23%
Toxic signs	27%

ous therapy. Results reported in the accompanying Tables, which are based upon this criterion, are, we believe, definitely conservative because of the number of intractable cases included.

RESULTS

Table 1 shows results obtained with PM 396 when the drug given immediately preceding PM 396 is used as a standard of comparison.

Analysis of the data in Table 1 shows that when the effectiveness of PM 396 is judged by using results of the drug given immediately preceding PM 396, complete control was obtained in 22% of the cases, practical control in 9%, and partial control in 29%. This analysis gives a superior effectiveness of PM 396 in terms of degree of seizure control of 60% beyond that of the previously administered drug and leaves 40% of the cases unchanged or worse.

As we mentioned above, we also used a placebo base line to test the effectiveness of PM 396, and results of this aspect of our study are given in Table 2.

Results given in Table 2 indicate that complete control was obtained in 17% of our patients, practical control in 17%, and partial control in 36% of all the patients treated, making a total of 70% receiving some benefit from PM 396, and only 30% remaining unaffected or worse. It is likewise apparent that, whereas the average number of seizures per week on a placebo regime was 108, on the drug immediately preceding PM 396 (Table 1) the average incidence of seizures per week for this group of patients was only 49 at the beginning of treatment with PM 396. Both these averages were reduced to 43 and 48, respectively, on PM 396. Our data seem to show that, on the whole, better results were obtained when PM 396 followed a placebo (no medication) than when it was immediately preceded by another experimental drug.

In summarizing results obtained by using these two different base lines (Tables 1 and 2), it may be seen that PM 396 gave good anticonvulsive action in a majority of our cases on a relatively small dosage. Degree of control within our various categories, however, differed widely, depending upon the type of base line used.

Our criterion of complete control is a very rigid criterion by which to judge the effectiveness of medication, since it is rare that persons suffering from seizures

TABLE 3.—*PM 334 (Milontin)—Complete Control*

Date	Cases Completely Controlled, %
2/51	30
7/51	27
12/51	24
5/52	21

remain seizure-free over long periods of time, and in the case of PM 334 we have had to revise our figures downward from time to time (Table 3).

When the category of complete control shows a decline, as in Table 3, it has been our experience that cases lost generally fall into the classification of practical control, an occasional seizure being present. We believe, therefore, that the classification of complete control is not very satisfactory a method for judging the effectiveness of any particular drug.

Further analysis of our present data on PM 396 indicates also that, in general, the type of base line used is relatively unimportant if the categories of complete control, practical control (80 to 99%), and partial control (5 to 79%) are grouped together, i. e., if some degree of control is considered. Some effectiveness was reached in 60 to 70% of our cases after treatment with PM 396, regardless of which base line is used. This grouping covers a wide range of seizure control (5 to 100%), however, and is of little value clinically, especially if most cases in the 5 to 79% range fall at the lower end of the category.

It seems to us, in reviewing our data, that the category of practical control (80 to 99%) becomes the crucial one, both statistically and clinically, in terms of interpretation. As in the case of PM 334, we expect to have to revise our percentage of complete control downward as time goes on, and we expect that most of these cases will eventually fall into the category of practical control when this is done.

Tentative results with PM 396 in a small series of patients with psychomotor seizures are given in Table 4.

While the number of cases is small (15) and the incidence of seizures per week low (7), Table 4 shows that complete control of psychomotor seizures for a minimum of four weeks was secured in 20% of the cases, practical control in 20% of the cases, and partial control in 40% of the total number of patients treated. Thus, only 20% of the patients with psychomotor seizures received no help from PM 396, and 80% of the patients improved.

DOSAGE

The average daily dose used in our series of petit mal cases was 1.1 gm., in units of 0.3 gm. capsules, or from 3 to 4 capsules a day. The range of effective dosage varied from 0.3 to 2.4 gm. daily, or from 1 to 5 capsules a day. The average effective dose of PM 334 was 2.7 gm. per day, thus showing that a much smaller

TABLE 4.—*Effect of PM 396 on Psychomotor Seizures*

No. of cases	15
Average no. of seizures per week on previous medication	7
Average no. of seizures per week on PM 396	2
Reduction in seizures	75%
Average daily dose, gm.	0.9
Average duration of treatment, wk.	15
Complete control	20%
Practical control (80 to 99%)	20%
Partial control (5 to 79%)	40%
No effect (0 to 4%)	20%
Condition worse	0%
Toxic signs	7%

TABLE 5.—*Incidence of Toxic Signs During Treatment with PM 396*

Rash	4
Drowsiness	4
Ataxia, dizziness	3
Vomiting	2
Loss of appetite	1
Loss of weight	1
Periorbital hyperemia	1

dose of PM 396 is required for effective therapeutic results. The upper dosage ranges of PM 396, i. e., above 2 gm. per day, are much more likely to produce nausea and vomiting than when PM 334 is used at these levels.

The average daily dose in the small series of psychomotor cases was 0.9 gm., or 3 capsules a day.

The technique of drug administration used here was identical to that used with PM 334; i. e., 0.3 gm. was given daily for one week and increased by 0.3 gm. each week if attacks were not controlled and toxic signs did not develop, until an average dose was reached, i. e., 3 to 4 capsules a day. All toxic signs, with the exception of drug rash, could usually be controlled by reducing the dose to a lower level. In the case of rash the drug was discontinued entirely.

TOXIC SIGNS

Toxic signs appeared in 11 cases, or 20%, of the series. These toxic signs are almost all of the same nature as those seen with PM 334, with the exception of a frank drug rash, seen in four instances, and periorbital hyperemia, seen in one

instance. The drug rash is rather similar to the rash of measles, and in two instances the similarity was so close that the differential diagnosis was not possible.

Table 5 shows the toxic signs in terms of frequency.

Rash and drowsiness were each seen in four cases, closely followed by dizziness, which was seen in three cases. The remaining toxic signs, especially vomiting, seem more prone to appear on relatively high doses.

To date, no blood dyscrasias have been noted, and all urines have remained normal.

SUMMARY

In our group of patients studied, N-methyl-α,α-methylphenylsuccinimide (PM 396) has been found to be an effective drug in the treatment of petit mal seizures, manifesting good anticonvulsant action and relatively mild side-effects.

Tentative results in a small series of cases indicate that PM 396 may also be beneficial in the treatment of psychomotor seizures.

We believe that PM 396 is an effective anti-petit-mal compound, prompt in its action, and an excellent addition to the growing armamentarium of petit mal drugs.

11 E. 68 St.

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FAMILIAL PERIODIC PARALYSIS, MYOTONIA, PROGRESSIVE AMYOTROPHY, AND PES CAVUS IN MEMBERS OF A SINGLE FAMILY

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THE ABUNDANT literature concerning "familial periodic paralysis" brings together a remarkable number of clinical phenomena in addition to experimental and laboratory findings that intrigue both clinician and biochemist. Considerable data relating mineral metabolism and a variety of endocrinopathies to diseases of muscle appear to begin to approach solution of the enigmatic problem presented by periodic paralysis and other diseases of muscle.

The present communication has as its purpose the documentation of a family who demonstrate a large number of different myopathic disorders. Furthermore, certain symptoms and signs presented suggest a combined heredity of myopathic and myelopathic or neuropathic disease.

REPORT OF THE O. FAMILY, A KINDRED COMPRISING FIVE GENERATIONS ON WHOM WE HAVE HISTORICAL AND CLINICAL INFORMATION

Seventeen persons in the O. family have been personally examined (numbered cases in fig. 1), and abstracts of clinical histories and neurological and laboratory examinations appear below. Cases 12 and 15, in addition to five other cases not personally examined whose histories do not appear in this report, were reported by Schoenthal in 1934.[1] The influence of thyroid extract on periodic paralytic attacks in seven members of this family was described by Wolf.[2] Data concerning other members of the family charted in Figures 1 and 2 were obtained from Patient 2, an intelligent and reliable witness.

Twenty-three persons in this kindred are known to have suffered periodic attacks of generalized muscular paralysis; 8 persons have developed a progressive wasting of skeletal muscles commencing in early adulthood; 5 persons developed pes cavus in childhood or early adolescence (independent of the progressive amyotrophy); 7 are reported to have displayed enlarged calf musculature in childhood; and 5 persons now have symptoms and signs of myotonia. One patient has had symptoms of (and successful neostigmine [Prostigmin] treatment for) an apparent myasthenia, in addition to periodic generalized paralysis, pes cavus, progressive muscular wasting, and myotonia. Areflexia of the lower limbs is present in six persons. Marked elevation of the longitudinal arch of the foot or hammertoes (contraction of extensor tendons of the pedal digits) is present in three persons without frank pes cavus or claw foot.

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REPORT OF CASES

CASE 1.—S. O., a 74-year-old woman, Polish-born. The father of the patient suffered periodic weak attacks; her first cousin displayed progressive muscular wasting, commencing in middle life. One sister (Case 12) has episodic paralytic attacks; two brothers are entirely well. The patient recalls earliest attacks at age 16 or 17. Duration was 10 to 15 minutes; occurrence was diurnal and nocturnal; attacks were unchanged by pregnancies but worsened following childbirth. Attacks were frequent until middle life and are now very rare. Patient may have momentary complete paralysis at night, lasting less than a minute. Precipitating factors are unknown. Patient suggests attacks are more likely "if I don't eat in time." Examination revealed a lively, well-developed, well-preserved woman. Blood pressure was 260/120. There were no gross muscle changes or myotonia. Ankle jerks were absent and the knee jerks diminished. There were bilateral hammertoes. No cataracts were discerned ophthalmoscopically.

CASE 2.—J. O., a 43-year-old male upholsterer. This man was first seen in the Grace-New Haven Community Hospital in 1924 at age 16, with the complaint of weak legs and progressive deformity of the feet of two years' duration. Reflexes were active; there were bilateral pes

Fig. 1.—O. family: Inheritance of periodic paralysis in five generations.

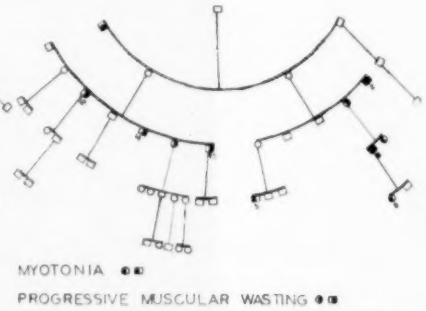

Fig. 2.—O. family: Inheritance of myotonia and progressive muscular wasting.

cavus, wide-based gait, and nystagmus in all directions of gaze. A diagnosis of Friedreich's ataxia was made. Subsequently, tenotomy and subastragalar arthrodesis were performed bilaterally.

1927: Patient complained on this visit of episodic weak spells since the age of four years, following strenuous exercise and emotional excitement. Migraine headaches had been present for several years. Examination disclosed diminished vibratory sense below the knees, absent deep tendon reflexes, and generalized myasthenia.

1940: Patient was admitted to another hospital for diagnosis and treatment of daily attacks of weakness without altered consciousness. Examination disclosed tapering lower limbs, awkward gait, loss of all deep and superficial reflexes, weakness of shoulder girdles, distal musculature of legs and erector spinae. There was bilateral von Graefe sign. A spontaneous weak attack was accompanied by loss of response to faradic stimulation save for upper trapezius. Laboratory data: basal metabolic rate normal, 24-hr. creatine/creatinine excretion 160/165 mg. per 100 cc. Profound generalized muscular paralysis was precipitated by simultaneous administration of insulin and glucose on one occasion, and on another by exertion followed by rest. Serum potassium measured 2.89 mEq. during attacks. Paralysis was not relieved by administration of 10 gm. of potassium chloride by mouth. Trial of a variety of drugs (potassium chloride, neostigmine, amphetamine [Benzedrine], quinine, calcium gluconate, magnesium sulfate, strong iodine solution U.S.P. [Lugol's solution]) was unsuccessful in ameliorating or preventing attacks. Parenteral neostigmine gave fairly good relief of individual attacks.

1950: Patient was studied by the neurological staff of a third hospital. Findings were essentially unchanged from 1940. Creatine/creatinine excretion measured 105/356 mg. per 100 cc. in 24 hours. Serum potassium was normal during mild spontaneous weak spells (not true attacks of generalized paralysis). A diagnosis of Charcot-Marie-Tooth disease and periodic paralysis was made. Patient was discharged unimproved, to take 10 gm. of oral potassium chloride daily.

1952: Patient discontinued potassium chloride after several months' trial because no relief was obtained from paretic attacks. Episodes of total paralysis were now rare; principal complaint was of chronic progressing muscular weakness plus episodic exacerbations of generalized or local weakness which were disabling for hours or days. During such attacks he was unable to rise from a chair unaided, climb stairs, or raise his arms above his head. Such attacks typically occurred during rest following exertion, and characteristically the muscles previously exercised were the first to lose power. Examination revealed a cooperative person of superior intelligence. General physical examination was within normal limits. There was moderate frontal balding

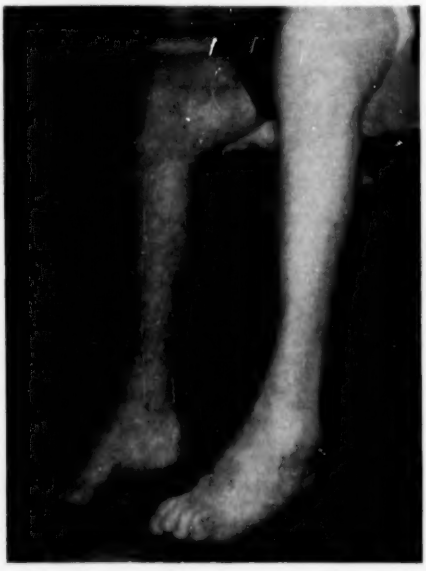

Fig. 3.—Patient 2 (J. O.): Pes cavus (partially corrected by surgery), wasting of musculature of lower extremities.

and no testicular atrophy. Ophthalmoscopic examination revealed indefinite lenticular changes. Examination by slit lamp (Dr. Andrew Wong) demonstrated definite incipient cortical cataractous changes. These were fine punctate opacities largely situated adjacent to the anterior and posterior capsule of the lens. There was bilateral pes cavus and atrophy of hamstrings, quadriceps femoris, tibial, and peroneal muscles (Fig. 3). There was no wasting of the facial muscles, sternocleidomastoids, or distal musculature of the upper extremities. The deep and superficial reflexes were absent and plantar responses were flexor. Vibratory sensibility was diminished below the knees. Gross fasciculations were noted in the right gastrocnemius and peroneal muscles. Myotonia was elicited from the tongue. Gait was steppage, not wide based, and no cerebellar signs or nystagmus were noted. There was no thickening of peripheral nerves to palpation. A positive Gowers sign (climbing with hands along legs when rising from floor) was present. Strength was approximately 50% of normal in the muscles of the shoulder girdles, the iliopsoas, and the abdominal musculature. Quadriceps femoris and peroneal muscle on the right retained about 40% of normal strength; those on the left, 80%. Muscle chronaxie in upper extremities

were normal. Chronaxie was impossible to evaluate in lower limbs owing to precipitation of continuous contraction fasciculations following a single stimulation of motor points. Electromyograms (1953, 1954) were interpreted by Dr. Gilbert H. Glaser as showing frequent intermittent single unit discharges from the resting peroneal muscle, indicating spontaneous fasciculations (Fig. 4).

Biopsy specimen from the right gastrocnemius muscle was examined by Dr. Raymond D. Adams, who submitted the following description:

"1. There is a very much greater variation in the size of muscle fiber than normal. My measurements showed them ranging from about 12 or 15 microns in diameter to 110 or 115. I saw no enormous fibers of a size that is clearly pathognomonic of dystrophy. There are some small clumps of sarcolemmal nuclei which may represent extremely atrophic fibers. In places all of the fibers are reduced to a subnormal size. These small ones tend to be grouped somewhat but in every place there are mixed with them a few large fibers. There are not many fields where one can judge this pattern. 2. Many of the normal-sized muscle fibers show centrally placed sarcolemmal nuclei. This is quite evident in cross-sections. In one group of about 20 fibers I found 3 with central nuclei. In longitudinal sections of the more atrophic fibers the sarcolemmal nuclei are relatively increased. In some places there are quite long rows of them,

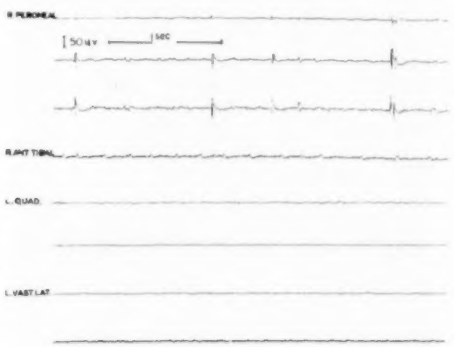

Fig. 4.—Patient 2 (J. O.): Electromyogram demonstrating single unit discharges from the resting peroneal and anterior tibial muscles.

the nuclei almost touching one another. These nuclei are rather dark and small and show none of the characteristic features of recent proliferative activity. 3. In places where the muscle is atrophic there is an increase in the endomesial and interstitial fat. This, of course, is in the form of cells. 4. There were two places where I thought there was some evidence of muscle fiber degeneration. The fiber appeared to be invaded by histiocytic elements. . . . The negative findings are lack of very conspicuous vascular change, little or no absolute increase in connective tissue, lack of proliferative activity of sarcolemmal nuclei or regeneration of sarcoplasm. . . . My suspicion would be that the case represents one of myotonic dystrophy. . . ." (Figs. 5 and 6.)

Serum potassium measured during spontaneous attacks of moderate weakness was consistently normal. Treatment with a variety of agents, including potassium citrate, 12 gm. daily, liver extract, vitamin B complex, vitamin B_{12}, Biohepulin,* neostigmine, glutamic acid, betaine glycocyamine (Betasyamine†) was uniformly unsuccessful in diminishing incidence of weak attacks. Oral cortisone administration was accompanied by a temporary (7-day) striking improvement in muscle strength and freedom from exacerbations of chronic weakness. Withdrawal of cortisone three weeks after it was begun was followed by profound generalized muscular weakness which lasted for two weeks. Intravenous administration of edrophonium (Tensilon) chloride

* Biohepulin, courtesy of International Biochemical Corp., Brooklyn, N. Y.

† Betasyamine, courtesy of International Minerals & Chemical Corp., Chicago.

during a spontaneous severe attack of weakness of the lower limbs was followed by onset of dysarthria and flushing but failed to relieve muscular weakness. Myotonia was impossible to elicit during attacks of spontaneous weakness. In 1954, this patient demonstrates progression of motor weakness and muscular wasting, most marked in the left quadriceps which is now nearly as disabled as the right. Exacerbations and remissions of chronic weakness continue to be the chief complaint.

CASE 3.—S. O., a 42-year-old man. Attacks of periodic weakness have occurred from the age of 2 or 3 years. These attacks are precipitated by exercise followed by rest. Attacks now occur only five or six times yearly and consist of total paralysis for about 30 minutes followed by five or six days of chronic myasthenia. Attacks were more frequent in adolescence and early adulthood, but complete recovery was much more rapid at that time (i. e., 30 to 40 minutes). Patient tried potassium chloride treatment years ago but consistently developed intense abdominal pain following ingestion of the salt and was never able to take medication regularly for as long as a week at a time. Thyroid preparations were not helpful. Examination disclosed a well-developed asthenic person whose muscles were unremarkable in appearance and consistency.

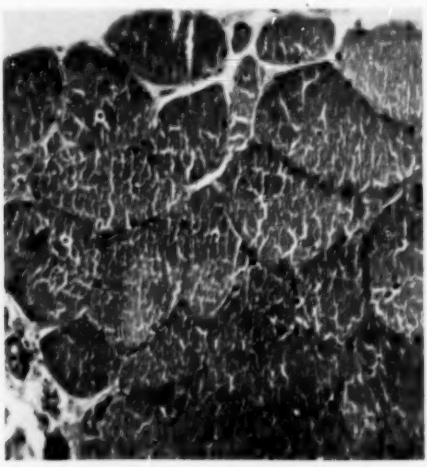

Fig. 5.—Patient 2 (J. O.): Cross section of gastrocnemius muscle demonstrating muscle fibers with centrally placed nuclei; × 233.

Hammertoes and pes planus were present. Patient could not walk on his heels or rise from a chair unaided. All reflexes were present and equal, and sensation was intact. There was myotonia of the tongue and thumb adductors in response to percussion. No balding, cataract, or testicular atrophy could be detected. Musculature of face, sternocleidomastoids, and hands was of normal bulk and strength.

CASE 4.—H. G., a 40-year-old woman. Patient has never experienced periodic attacks of weakness. "Foot trouble" has been present since adolescence. Examination disclosed high-arched feet, hammertoes, early cavus deformity, and absent knee and ankle reflexes. Vibratory sensation was absent in the toes and diminished in the knees. There was no atrophy, weakness, or myotonia. Examination of the eyes by the slit lamp (Dr. Wong) failed to reveal any abnormality of the lens.

CASE 5.—A. G., a 15-year-old boy. No paralytic attacks have ever occurred. This boy complains of feeling "tired all the time" but is otherwise entirely well. Examination revealed a cooperative lad of superior intelligence, with normal muscular development. Feet were high-arched, with clawing of the toes. The deep tendon reflexes in the lower extremities were hyperactive, with suggestive extensor plantar reflexes bilaterally. No cerebellar signs, myotonia, or sensory loss was detected.

CASE 6.—K. G., an 11-year-old boy. No weak spells have occurred. Since the age of 3 or 4 increasingly high-arched feet have caused progressive difficulty in ambulation. The feet were surgically corrected in 1954. Examination prior to operation revealed obvious pes cavus deformity bilaterally, the right more than the left. Deep reflexes were absent in the lower extremities, and there was diminished vibratory sense in the toes. No myotonia was present and no cerebellar signs were elicited. The testicles were undescended.

CASE 7.—M. G., a 3-year-old boy. No attacks of weakness have occurred. Examination was within normal limits.

CASE 8.—H. H., a 34-year-old man. The patient has noted episodic spells of muscular weakness since early childhood, characteristically following exercise or heavy meals. Spells last up to one hour and usually consist of total paralysis of voluntary muscles. Calves were allegedly enlarged in childhood. When the patient was about 16 years of age, he noted difficulty in initiating motion after brief rest. This condition was relieved after moving muscles for a

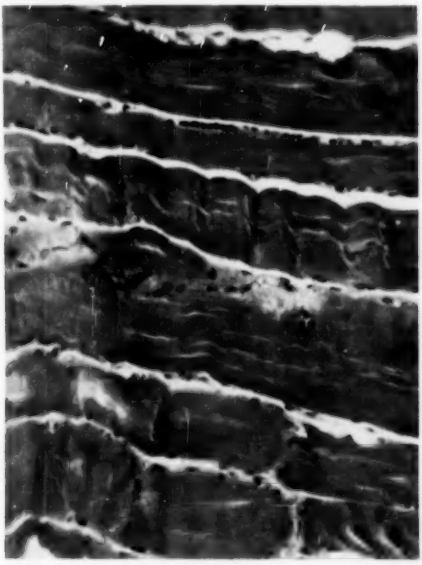

Fig. 6.—Patient 2 (J. O.): Longitudinal section of gastrocnemius muscle demonstrating variation in fiber size and relative increase in sarcolemmal nuclei; × 233.

few moments, and was entirely relieved by ingestion of quinine. At age 17 patient was hospitalized in New York; examination at that time disclosed generalized hyporeflexia, absent deep reflexes in the lower extremities, pes cavus, von Graefe's sign, hypertrophy of sternomastoid muscles, and prolonged myotonic response to muscular percussion. A diagnosis of Thomsen's disease (myotonia congenita) was made. The following year, ptosis of the eyelids developed and was allegedly relieved by injections of neostigmine. The patient was examined in the Grace-New Haven Community Hospital in 1952. Spells of muscular weakness were now rare. However, the patient complained of chronic persistent weakness of the legs, which had commenced in his late teens and was gradually increasing in severity, now causing marked difficulty in walking and climbing stairs. At age 32 severe weakness and numbness of the arms and legs developed rather suddenly and partially and gradually cleared three or four months later. Examination, in 1953, revealed a well-developed and intelligent person. Gait was slapping with steppage, and the Romberg sign was positive. There was bilateral moderate ptosis of the eyelids. The thyroid gland was not palpable. There was marked myotonia with delayed release of grip and prolonged

contraction following percussion of glossal and skeletal musculature. Deep reflexes in the lower extremities were absent. Position sensation was lost in the toes and vibratory sensibility was absent below T11. A surgically corrected pes cavus deformity was present bilaterally. There was thinning of the peroneal, tibial, and calf musculature bilaterally and bilateral foot drop (Fig. 7). Electromyograms disclosed both spontaneous single motor unit discharges (fasciculations) at rest in the calves and prolonged myotonic responses following voluntary contraction of muscles in all four limbs. The myotonic phenomenon is demonstrated electromyographically in Figure 8.

Case 9.—M. H., a 7-year-old girl. The first attacks of total muscular paralysis followed this patient's second birthday. Weak spells are now induced by remaining a long while in one position. They are commonest in the early morning, the frequency varying from daily to every two to three weeks. The duration of weak attacks is usually less than an hour. Examination disclosed enlarged calves, depressed ankle jerks, and mild myotonic response to percussion of the tongue.

Fig. 7.—Patient 8 (H. H.): Drop foot, surgically corrected cavus deformity, and peripheral muscular wasting.

Case 10.—S. H., a 1½-year-old boy. No symptoms of neuromuscular disease were present and examination was entirely within normal limits.

Case 11.—J. X., an 80-year-old woman. The patient suffered periodic attacks of generalized muscular weakness commencing in girlhood, but these have been rare since middle age. Cataracts were removed at 60 years of age. Detailed history was not available from the patient due to deterioration of her mental state. Examination disclosed a confused elderly person suffering from a senile type of mental deterioration. There was no gross muscular disease or orthopedic deformity.

Case 12.—H. X., a 59-year-old man. This man suffered episodic weak attacks beginning about the age of 2 years, occurring typically at night after exercise or ingestion of a meal high in carbohydrate. Attacks consist of complete paralysis, including the face, with a duration up to 25 minutes. The patient "works off" attacks by trying to keep moving actively at the first

sign of muscular weakness. Attacks are definitely precipitated by the rest following muscular exertion and never occur during actual exercise. Calves were said to be enlarged in childhood and then to diminish in size during adolescence. At age 40 he began to note progressive chronic weakness of the legs. Treatment with potassium salts, amphetamine, and thyroid preparations were unsuccessful in preventing attacks of weakness. Examination disclosed a well-developed and intelligent adult. There was moderate weakness without obvious atrophy of the peroneals, biceps, and abdominal muscles. Both triceps retained approximately half of normal strength. The gait was stiff, with slapping of the feet. Sensation was intact. The feet were high-arched but not otherwise deformed. Reflexes were intact. There was no myotonia elicited and ophthalmoscopic examination failed to reveal lenticular abnormality.

Case 13.—J. P., a 50-year-old woman. This woman began to have episodic attacks of total paralysis (sparing the tongue, face, and respiratory muscles) at the age of 2 years. Attacks were nocturnal or diurnal and were typically precipitated by exertion followed by rest. Attacks are

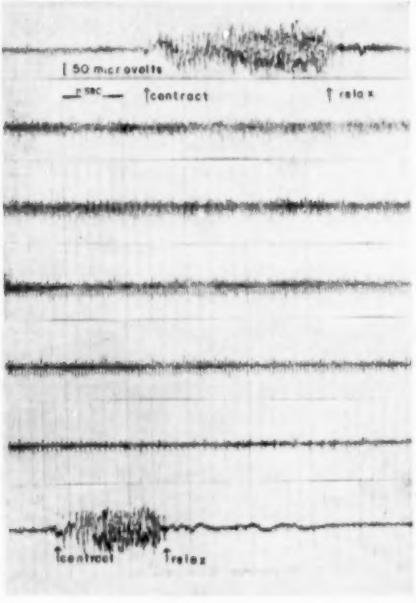

Fig. 8.—Patient 8 (H. H.): Electromyogram demonstrating delayed relaxation of quadriceps muscle following brief voluntary contraction, followed by prompt relaxation after second voluntary contraction.

now less frequent than in her youth but do occur if she overexerts herself and then rests a long while. Duration of attacks is 15 to 45 minutes. The patient can "walk off" attacks, if she exercises as soon as the prodromal muscular "stiffness" begins. Examination revealed a well-developed intelligent person with normal musculature and reflexes. Vibratory sense was diminished in the toes. There was no evidence of myotonia or cataract (ophthalmoscopic examination only).

Case 14.—Bo. X., a 46-year-old man. Since the age of 2 years this man has noted episodic paralytic attacks which occurred approximately twice weekly in his youth, lasting 30 to 45 minutes. Paralysis was total save for the respiratory and facial muscles, which were spared or only slightly affected. Deglutition was often difficult. For the past 15 years attacks have occurred approximately once weekly, but are now mild, and he is always able to move weakly. Attacks are often precipitated by emotional upsets. There has been progressive chronic weakness

of the legs since the age of 17 years. Examination disclosed a well-developed man with obvious atrophy of medial sternomastoids and serratus anterior, and moderate atrophy of the trapezii and thighs. The calves were relatively large as compared to the thighs. There was marked weakness (less than 50% of normal function) of tibials, toe flexors and extensors, and quadriceps femori. Hamstrings, iliopsoas, triceps, and neck flexors exhibited moderate to marked weakness. Facial expression and musculature were normal. The deep reflexes were all sluggish and the right knee jerk was absent. There was no myotonia or cataract (ophthalmoscopic examination only). Pinprick sensibility was slightly diminished in the feet.

CASE 15.—Bi. X., a 44-year-old man. The patient has had episodic spells of weakness, largely nocturnal, since early childhood. The attacks lasted 15 minutes to 48 hours and were occasionally associated with blurred vision. Muscular weakness was generalized and profound. These attacks diminished in frequency in his 20's, and none have occurred during the past five years. However, there has been progressive slowing down of all muscular abilities since the early 20's, particularly noted in climbing stairs, walking distances, and rising from the seated position. There are intermittent exacerbations of mild generalized weakness without paralysis lasting for many days at a time. This state is described by the patient as an "all gone" feeling. Calves are said to have been enlarged in childhood. Examination disclosed a well-developed intelligent person, with enlarged calves and generalized muscular weakness most marked in triceps, biceps, extensors hallucis, and anterior tibials. The gait was stiff, with slapping of the feet. There was slight but definite decrease in pinprick appreciation in the feet and lower legs. There was no marked muscular atrophy or orthopedic deformity. Neither myotonia nor cataract was present.

CASE 16.—S. X., an 8-year-old boy. The boy has had severe attacks of generalized flaccid muscular paralysis of 15 to 60 minutes' duration since the age of 2 years. These attacks have without exception occurred during sleep. Examination revealed an active, bright child who was physically and neurologically unremarkable.

CASE 17.—R. X., a 4-year-old boy. The boy has had no attacks of muscular weakness and no other disabilities are reported. Examination was normal.

In summary, this rather remarkable family appears to represent a meeting point of a number of elements in the muscular dystrophy constellation. As a group these persons appear to bear witness to the hypothesis of Aring and Cobb [3] that the various hereditary muscular dystrophies are not unrelated. In addition, evidence of neuropathic (electromyograms, sensory disturbances, reflex loss) as well as myopathic taint is present. Members of this kindred have intermittently or progressively exhibited the following symptoms and signs: an ataxic disorder with progressive amyotrophy, pes cavus, nystagmus, peroneal wasting, and signs of posterior spinal column involvement (Case 2), less completely expressed (formes frustes) by pes cavus and reflex or sensory changes or merely high-arched feet and "hammertoes" (Cases 1, 4, 5, 6, 8, 12, and 13); myotonia (Cases 2, 3, 8, and 9) followed by chronic muscular wasting in two cases (Cases 2 and 8) but lacking most of the other features of the dystrophia myotonica syndrome; episodic apparent myasthenia allegedly responsive to neostigmine (Case 8); calf enlargement in childhood followed by gradual muscular wasting, involving proximal muscles early but frequently accompanied by peripheral atrophy as well (Cases 2, 3, 8, 12, and 14). Periodic attacks of partial or total flaccid paralysis have characterized the childhood and young adulthood of all persons suffering muscular wasting, but this is not true of those developing pes cavus or allied milder deformities of the feet. The occurrence of periodic paralytic attacks has not regularly been followed by muscular wasting in later life. Myotonia is not demonstrable in all persons with amyotrophy.

The attacks of muscular weakness here described are briefer in duration than those occurring in the majority of cases of familial periodic paralysis reported in the literature.[4] Rarely do members of this family note total muscular paralysis of

a duration beyond two hours. In the majority of instances, attacks of paralysis are of 15 to 45 minutes in length. The failure to prevent or abort attacks by ingestion of potassium salts is less unusual and has been recently discussed by Tyler and coworkers.[5] In addition to episodic attacks of total paralysis, the primary complaint of adult periodic paralytics in this family is of waxing and waning of chronic partial weakness, exacerbations of generalized or local weakness being characteristically precipitated by exertion followed by rest and typically occurring primarily in muscles previously subjected to exertion. These spontaneous exacerbations of weakness are not associated with low serum potassium.

Coexistence of periodic paralysis with various other muscular disorders in a single person or family is well known. Symptoms suggestive of myasthenia gravis were reported in such a family by Taylor [6]; progressive muscular wasting late in the course of periodic paralysis was noted in families reported by numerous observers.‡ Enlargement of muscles has also been described in periodic paralysis families.[8] Bernhardt [12] has described several members of a family suffering brief paralytic attacks who had enlarged limb musculature and change in muscle power related to cold. True myotonia is not described. Appearance of pes cavus, myotonia, intermittent cerebellar signs, and sensory disturbances in patients presenting the periodic paralysis syndrome is unknown to us. That this family may represent a coincidental inheritance of multiple separate genetic traits rather than of variety in expression of a single genotype is of course possible.

The primary locus of lesions causing the pes cavus deformity is not agreed upon. That bone and joint structure is normal is generally accepted. Yakovlev § considers probable origin of the deformity to be related to a disturbance in the tonic innervation of the foot. The neurologist most frequently sees this deformity in association with Friedreich's spinocerebellar ataxia and other disorders involving central or peripheral innervation of the foot. As Wilson [13] has pointed out, families displaying the Friedreich traits not infrequently demonstrate variations which appear to link this syndrome to a variety of other neurological and muscular disorders. Accompanying muscular dystrophy, pseudohypertrophy, and peroneal atrophy have been described in such families. Slightly affected members of families suffering from Friedreich's disease may demonstrate only reflex loss or conversely hyperactive reflexes with extensor toe sign, high-arched feet, or contracture of extensor tendon of the hallux ("hammertoe"). Spillane,[14] among others, has suggested the genetic identity of the Friedreich, Charcot-Marie-Tooth, and Roussy-Lévy syndromes.

It is not easy to overlook the possible relationship of the above-reported kindred to the Friedreich group. One patient (Case 2) is reliably reported to have demonstrated nystagmus at the time pes cavus was first noted. All degrees of the cavus deformity occur in other members of the kindred. Reflex alteration in the absence of gross muscular wasting or weakness strongly suggests a neuropathic as well as a myopathic taint in this family. Electromyographic studies confirm this suspicion, giving evidence of neural or spinal disorder as well as conforming to descriptions of myotonic disease ‖ (Cases 2 and 8).

‡ References 7 through 11.

§ Yakovlev, P. I. Y.: Personal communication.

‖ References 15 through 18.

True myotonia, as noted in four patients of this kindred, is commonly recognized in only two neuromuscular syndromes, myotonia congenita (Thomsen's disease), in which enlargement of muscles is common and wasting or weakness is absent, and myotonia dystrophica, in which the latter are prominent.[19] That these disorders may be related has been suggested.¶ There is also much evidence against such a relationship.[22] The family here reported demonstrates features of both Thomsen's disease and dystrophia myotonica. Enlargement of muscles, particularly calves, in childhood and youth was noted in four of the patients demonstrating myotonia on examination. Two of these patients (Cases 3 and 8) have developed muscular wasting in early middle life. However, the location of muscular wasting is not at all typical of myotonic dystrophy, the muscles of the face, the hands, and the sternomastoids being regularly spared. The other defects (cataract, testicular atrophy, alopecia, mental deterioration) so characteristic of myotonic dystrophy are also in large part absent, although slit-lamp examination disclosed lenticular changes in one member of this family (Case 3). Peripheral sensory disturbance (vibratory sensibility) has been reported in patients with myotonic dystrophy [23] and is not considered to be incompatible with that diagnosis, although its cause remains obscure. Rare cases of so-called myotonia paradoxica [24] and Talma's myotonia acquisita [25] have been recorded, but the family here reported does not conform to descriptions of these disorders.

The presence of myotonia only in persons with periodic attacks of flaccid generalized muscular paralysis, as in the four patients here reported, is of particular interest. Zabriskie [26] has reported delayed "decontraction" of musculature in a patient with periodic paralysis. This condition was accentuated by cold but not associated with increase in muscular irritability. We prefer to consider the myotonia present in certain members of this family as a manifestation of the wide disturbance in muscle function here apparent. While not falling easily into any of the known myotonic clinical entities, links with both myotonia congenita and dystrophia myotonica suggest that the symptom of myotonia may be a nonspecific manifestation of disordered muscular function. Since potassium is known to worsen myotonia,# it is of interest to speculate on the lack of favorable response to potassium salts in members of this family suffering from periodic flaccid paralytic attacks. On the other hand, no member of this family reported worsening of myotonia while receiving large amounts of potassium by mouth.

Demonstration of the relationship of the serum potassium level to attacks of periodic paralysis * has opened the way to considerable clinical research concerning the pathogenesis of the paralytic attacks. That severity of either induced or spontaneous paralytic attacks does not coincide with the lowest point on the serum potassium curve is now well known.† Indeed, relatively high levels of serum potassium may be demonstrated at the height of paralysis, the relative fall in potassium level being as little as 5%. No consistent or absolute level of serum potassium

¶ References 20 and 21.
# References 27 and 28.
* References 8 and 29.
† References 30 and 31.

is associated with the incidence or severity of attacks. Flaccid paralysis in persons with the periodic paralysis trait occurs at much higher levels of serum potassium than in persons not carrying this genetic tendency.

Fall in serum potassium, when it does occur, is not accompanied by increased excretion of potassium by the kidney. Indeed, urinary potassium falls prior to and during the attack and is not increased after attacks.‡ Circulating erythrocytes also fail to show increased potassium content prior to, during, or after attacks.[32] Hence, migration of potassium from the serum must be to some other reservoir, the most likely possibilities being muscle or liver.

Sleep, heavy meals, and muscular exertion followed by rest are the historical factors most commonly related as precipitants of paralytic attacks both in the family reported here and in the majority of such families documented in the literature. Following strenuous muscular exertion (convulsive seizures) potassium, which leaves the cells during exercise, returns to the intracellular phase in greater concentration than in the previous resting state.[34] Heavy caloric intake has a similar effect on potassium ratios, the intracellular shift of potassium presumably being related to the role of the potassium ion in glyconeogenesis. The precipitation of paralytic attacks by sleep is less easily subject to interpretation. We are particularly interested, with reference to the family reported here, in the role of prolonged maintenance of fixed body positions (as in sleep) to the production of both flaccid paralytic and myotonic episodes. Both epinephrine and desoxycorticosterone are agents which depress potassium and predispose to paralytic attacks. Nevertheless, these agents also abolish the myotonic phenomena.[28]

In summary, both clinical and experimental factors have in common a relative depletion of serum potassium as a possible factor in the precipitation of periodic paralytic attacks. However, since no absolute level of serum potassium is correlated with onset of or severity of attacks (quite unlike the paralysis accompanying metabolic hypokalemias which consistently demonstrate a very marked depletion of serum potassium), factors other than the absolute serum potassium level must be supposed to be of major importance in persons carrying the periodic paralysis trait.

Potassium is successful in treating a certain number of patients suffering from typical familial periodic paralysis. As noted by Tyler and co-workers,[5] it is not unfailingly so. In the family documented above, oral potassium administration in high dosage caused unpleasant side-effects (lumbar and abdominal pain) and did not prevent attacks. The occurrence of abnormal serum potassium depletion following exercises in patients with myotonic dystrophy has been reported by Cumings and Maas.[35] The presence or latent presence of myotonia in this family of periodic paralytics may be a factor in the failure of response of paralytic attacks to potassium therapy.

From a group of studies concerning potassium relationships in myasthenia gravis, Cumings § has demonstrated a significant relationship between muscular weakness and muscular potassium content in that syndrome. He has shown that muscle potassium is abnormal in two neuromuscular diseases (excluding muscles

‡ References 32 and 33.

§ References 36 through 40.

in which extensive atrophy and fibrosis have occurred). Muscle potassium is elevated in myasthenia gravis and depressed in myotonia. Administration of neostigmine to the myasthenic is accompanied by a fall in muscle potassium with concomitant (very small) rise in serum potassium. Fall in muscle potassium is coincident with improvement of muscle strength and is followed by return to abnormally high levels as the effect of neostigmine disappears. Similar studies have not yet been carried out in the case of periodic paralysis. If a hypothetical parallel to myasthenia gravis be admissible, it is possible that the potassium ion upon leaving the circulation enters muscle during attacks of paralysis. Shift in serum potassium level may be only from upper to lower levels of normal, the lowered serum potassium being less significant than the rise in muscle potassium. This may also prove a link between periodic paralysis and myotonia, the depletion of intramuscular potassium being of significance in the latter. In our experience as well as in that of others,‖ periodic paralysis may demonstrate a therapeutic response to neostigmine. Similarly, potassium is occasionally a helpful adjunct to the neostigmine treatment of myasthenia gravis.

The striking clinical differences between myasthenia and periodic paralysis—precipitation by exertion of the former, by rest in the latter; involvement of nearly opposite muscle groups, viz., large proximal muscles in periodic paralysis and sparing face, respiratory, and ocular muscles, while the latter are precisely the groups involved primarily in myasthenia gravis—may be a clue of related pathogenesis.

In myotonic muscle Cumings [37] has found a marked diminution of potassium. After neostigmine administration, myotonic muscle potassium increases toward a normal figure (a directly opposite result to that obtained following neostigmine treatment of myasthenics). Blahd and associates [44] have demonstrated a significant decrease in exchangeable potassium ion in myotonia congenita, as well as in other diseases of muscle.

As Aring and Cobb [3] have pointed out, the high incidence of endocrinopathies appearing in the gamut of hereditary muscular disorders compels one to consider a possible etiological relationship between the two. Equally provocative is the widespread evidence of muscular affection in endocrine disease, e. g., unexplained and severe muscular weakness in adrenal cortical hypofunction (Addison's disease), the Cushing syndrome, and anterior pituitary insufficiency; amyotrophy, myasthenia, and periodic paralysis in the course of thyrotoxicosis ¶; the relationship of thymoma to myasthenia gravis; the occurrence of pseudomyotonia and muscular enlargement in the presence of toxic diffuse goiter (Basedow's disease).[22] Evidence of disturbed water balance regulation (manifested by anuria, polyuria, diaphoresis) in many patients with periodic paralysis has led several investigators to invoke a hypothalamic-hypophyseal etiologic basis for the syndrome.#

Although exhaustive metabolic surveys [30] fail to disclose any hint of primary metabolic dysfunction in muscular dystrophy patients, it is possible that examinations still to be devised may uncover such a defect. Histological examination has

‖ References 41 through 43.

¶ References 45 through 48.

References 47 and 49.

reportedly disclosed degeneration of cells in hypothalamus and certain portions of the brain stem in patients with myotonia congenita.[5] Electroencephalography has demonstrated no abnormality in a single case of periodic paralysis.[52]

SUMMARY

Historical and clinical data concerning 17 members of a kindred suffering from a remarkable number of possibly associated myopathies are presented. Progressive muscular wasting, both proximal and distal, pes cavus, calf hypertrophy, myotonia, periodic paralysis, sensory disturbances, and symptoms of myasthenia gravis have been found in members of this family. Although a single muscle biopsy suggests myotonic dystrophy, most elements of this syndrome are lacking. The relationship of the hereditary muscular dystrophies is briefly discussed. There is some evidence that a hereditary central neuroendocrine factor may underlie these various syndromes. Alterations in potassium content of serum or muscle in certain of these states (periodic paralysis, myotonia, myasthenia gravis) may be only an expression of such a central defect, which has thus far eluded measurement by other means.

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ALTERNATING CONTRACTION ANISOCORIA

A Pupillary Syndrome of the Anterior Midbrain

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AMONG THE clinical cases examined in this laboratory a relatively large group showed a pupillary syndrome which I have named alternating contraction anisocoria. I have used the term contraction anisocoria in order to describe the appearance of inequality of the pupils under the influence of a pupilloconstrictor stimulus, such as light, while the term alternating is used because there is a variation as to which pupil becomes smaller. In alternating contraction anisocoria the pupil of the stimulated eye always contracts more extensively than does the consensually reacting pupil of the opposite side.

Many neurologists and ophthalmologists believe that pupillary inequality due to uneven illumination is a physiological phenomenon. Pupillographic records do not agree with this view. Apparent inequality of the pupils results from an optical illusion on the part of the observer, whereby the pupil of the dimly lighted eye seems larger than that of the brightly illuminated one. Furthermore, unrecognized pathological conditions may cause anisocoria, for example, the frequently occurring peripheral sympathetic condition.

Alternating contraction anisocoria is a fleeting phenomenon, usually of small extent. It generally escapes ordinary observation and can be revealed with certainty only with the aid of pupillographic records.

METHOD

Pupillography is the recording and analysis of pupillary movements and reflexes under standard conditions. For a detailed description of the technique the reader is referred to the literature.*

The clinical routine examination used in this laboratory consists of the following series of reactions, with periods of rest interposed.

SERIES 1.—After adaptation to dark red-infrared illumination for at least six minutes, two reactions to light are elicited in which both eyes are simultaneously exposed to the stimulating light. The stimulus intensity is "standard," e. g., 15 f.-c. (foot-candles) through a Wratten X1 green filter, the duration being one second and the dark interval between stimuli three seconds.

SERIES 2 and 3.—The right (Series 2) or left (Series 3) eye alone is exposed to seven consecutive light stimuli, while the other eye remains in darkness. Stimulus intensity, duration, and frequency are the same as in Series 1. A psychosensory stimulus, such as sudden sound, is interposed between the fourth and fifth light stimuli of each series.

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* References 1 through 3.

SERIES 4 and 5.—The right (Series 4) or left (Series 5) eye is exposed to low intensity light stimuli (0.2 to 0.3 f.-c.). The duration and frequency of these stimuli are the same as above.

SERIES 6.—Two reactions to near and distant vision are recorded.

SERIES 7 and 8.—After the right eye (Series 7) or the left eye (Series 8) is adapted for at least three minutes to the 15 f.-c. green stimulating light, three darkness stimuli are given. They are one-second interruptions of the green stimulating light, with light intervals of three seconds.†

DESCRIPTION OF THE SYNDROME

Alternating contraction anisocoria may be unilateral or bilateral and either pure or complicated by additional pupillary pathology.

I. *Unilateral Syndrome* (Fig. 1).—In the unilateral syndrome, the pupils remain equal during light stimulation of one eye but they become unequal when the other eye is illuminated. This condition is shown in Figure 1. After six minutes of adaptation to dark red-infrared illumination, the pupils are equal at 7.7 mm. (Fig. 1, *a*). When the right eye is stimulated by standard intensity light (Fig. 1, *b*), the right and left pupils contract and redilate equally. The extent and shape of the reflex are normal. When under the same conditions the left eye is stimulated by light (Fig. 1, *e*), the consensually reacting right pupil lags behind the directly reacting left one, thus showing a contraction anisocoria. During the redilation period the pupils again become equal.

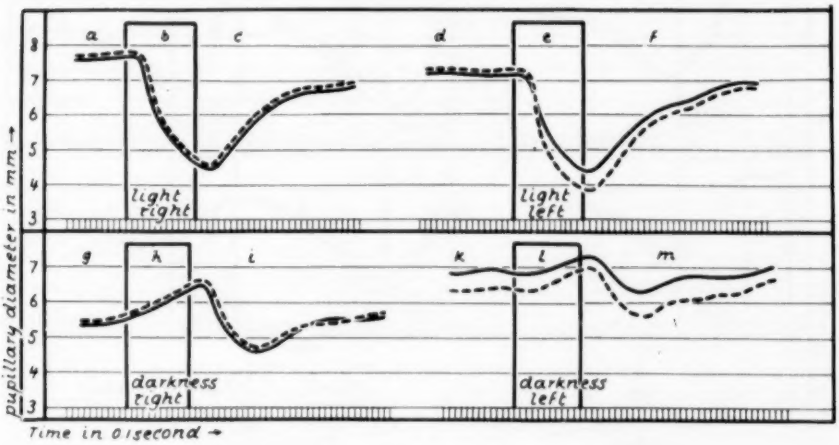

Fig. 1.—Unilateral syndrome of alternating contraction anisocoria (uncomplicated). The pupillary diameter (in millimeters) is plotted as the ordinate against time (in 0.1 second) as the abscissa. The solid line represents the right pupil; the broken line, the left pupil.

First Line: The pupils are equal in darkness (*a* and *d*). When the right eye is exposed to a standard intensity light stimulus (*b*), the two pupils contract and redilate (*c*) normally and equally. On the other hand, when the left eye is stimulated by the same light (*e*), the direct reaction of the left pupil exceeds the consensual reaction of the right pupil, and so the left pupil becomes smaller than the right one (*e*).

Second Line: Similar behavior is shown in the darkness reflex series. When the right eye is adapted to the 15 f.-c. light (*g*), the pupils remain equal, but they become unequal when the left eye is adapted to the same light (*k*).

† The darkness reflex should not be confused with the dark adaptation process.

A similar behavior is seen when the reflex to darkness is elicited. The pupils remain equal at a diameter of 5.5 mm. when the right eye is adapted to the standard intensity stimulating light (Fig. 1, *g*), and the two pupils react normally and equally to darkness stimulation (Fig. 1, *h* and *i*). In contrast, adaptation of the left eye to the standard intensity light causes the left pupil to become smaller than the right one. In addition, both pupils are larger when the left eye is adapted to light (6.3 and 6.9 mm., Fig. 1, *k*) than when the right eye is adapted (5.5 mm., Fig. 1, *g*). This last feature is often, but not always, found in the syndrome.

II. *Bilateral Syndrome* (Fig. 2).—The bilateral syndrome differs from the unilateral in that dynamic contraction anisocoria results from light stimulation of either eye. The direct reaction of the stimulated eye always exceeds the consensual reaction of the opposite eye. Figure 2 shows such a case.

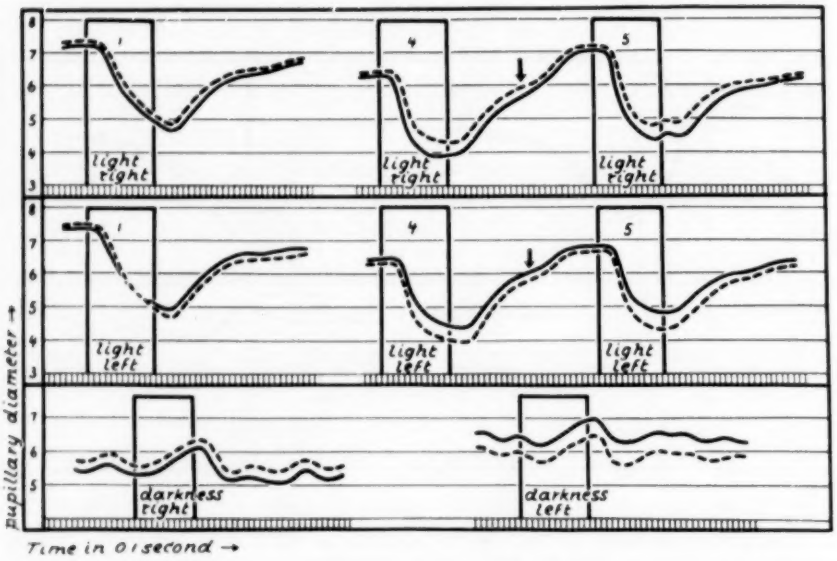

Fig. 2.—Bilateral syndrome of alternating contraction anisocoria (uncomplicated).

The pupillary diameter (in millimeters) is plotted against time (in 0.1 second). The solid line represents the right pupil; the broken line, the left pupil. The arrows of Lines 1 and 2 indicate the moment of elicitation of a sound stimulus. The first, fourth, and fifth light stimulations are shown in a sequence of seven stimulations.

First Line: In darkness the pupils are equal, but they become unequal during a series of light stimuli to the right eye; the right pupil becomes smaller than the left one because its direct reactions are more extensive than the consensual reactions of the left pupil. The shape and extent of the light reflexes as well as of the psychosensory reflexes are otherwise normal.

Second Line: When the left eye is stimulated by light, the direct reaction of the left pupil exceeds the consensual reaction of the right pupil. Consequently, the left pupil becomes smaller than the right one.

Third Line: Similar results are found in the darkness reflex series. The right pupil is smaller than the left one when the right eye is adapted to light, but it is larger than the left one when the left eye is adapted to light, while the shape and extent of the reflexes are within normal limits.

Bilateral alternating contraction anisocoria is rarely symmetrical. It is usually more pronounced upon stimulation of one eye than upon stimulation of the other.

III. *Complicated Alternating Contraction Anisocoria.*—The syndrome may be complicated by additional pathological features. Such complications may originate from any other site along the pupillary reflex pathways.

IV. *Occurrence.*—A group of 690 clinical cases of all kinds was used for this presentation. The only basis for selection from the clinical material available in this laboratory was that they were all examined with the same intrument. In this material the syndrome was found 158 times, which is about one-fourth of the total number (22.9%).

Of the 158 cases showing the syndrome, more than two-thirds (108) were unilateral and almost one-third (50) were bilateral. About one-third (52) showed the uncomplicated syndrome, and about two-thirds (106) showed it complicated by other pupillary pathology. These complications, in the order of their frequency, are third nerve nucleus or peripheral third nerve lesions (53); interbrain lesions (47);

TABLE 1.—*Analysis of Cases*

	Unilateral	Bilateral	Number Total
Cases with the pure alternating contraction anisocoria syndrome	31	21	52
Cases in which the alternating contraction anisocoria syndrome was complicated by one or more pupillary symptoms	77	29	106
Total number	108	50	158
Causes of complication			
(*a*) Peripheral sympathetic lesions	11	6	17
(*b*) Interbrain lesions	34	13	47
(*c*) Third nerve nucleus or third nerve lesions	28	25	53
(*d*) Clinically apparent lesions in optic nerve, chiasm, or tract	32	7	39
(*e*) Cases with more than one lesion	28	6	34

lesions of the optic nerve, optic chiasm, or optic tract (39), and postganglionic or preganglionic peripheral sympathetic lesions (17). About 20% (34) of the cases showed alternating contraction anisocoria complicated by more than one additional lesion.

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

Although localization of the lesion responsible for alternating contraction anisocoria appears at first glance to be a simple matter, it actually presents great difficulties.

If, in accordance with the terminology used in an earlier paper,[4] the intraretinal neurons are disregarded, the light reflex arc is composed of four neurons:

1. The "first neuron," i. e., the retinal ganglion cell layer, sends its fibers through the optic nerve, optic chiasm, and optic tract to the right and left pretectal areas in the anterodorsal midbrain.

2. The "second neuron" transmits the stimuli received by each pretectal area to the right and left Westphal-Edinger nuclei.

3. The "third neuron" consists of the preganglionic third nerve fibers from the Westphal-Edinger nucleus to the ciliary ganglion.

4. The "fourth neuron" is composed of the postganglionic short ciliary fibers to the iris sphincter.

The first and second neurons are also referred to as afferent neurons, while the third and fourth are efferent.

Previous work ‡ indicates that the lesion causing alternating contraction anisocoria cannot be located in the first neuron, because in man uncomplicated lesions of the optic nerve, optic chiasm, and optic tract do not result in anisocoria. Lesions in the first neuron lead to the reduction of the reaction to light, and the reflex pattern is changed to characteristic low intensity shapes; but the two pupils always act in unison and, barring additional damage to other pupillary neurons, the reactions cannot be distinguished from those found in normal man in response to low intensity light stimuli.

The lesion can be located neither in the third nerve nucleus nor peripheral to it. Damage to the efferent neurons on one side or the other would result in contraction anisocoria, since the pupil on the side of the lesion would react less extensively

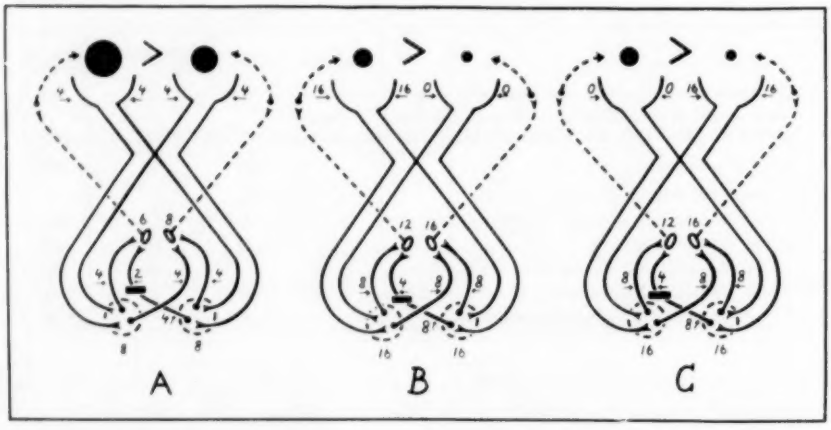

Fig. 3.—Three samples of calculations of the effect of a lesion in the second afferent neuron of the light reflex arc.

One-half of the crossed fibers from the right pretectal area to the left third nerve nucleus are assumed to be damaged.

A: Both eyes are illuminated by diffuse light of 4 f.-c. intensity per retinal half. Each pretectal area receives a stimulation value of 8, of which 4 comes from the homolateral eye via uncrossed optic fibers and 4 come from the opposite eye via crossed fibers. In the second neuron, half the pretectal fibers cross in the posterior commissure to reach the opposite third nerve nucleus, while the other half remain uncrossed. Normally, therefore, each third nerve nucleus would receive a total stimulation value of 8. But since one-half of the crossed fibers from the right pretectal area to the left third nerve nucleus are interrupted, the left third nerve nucleus receives a stimulation value of only 6. Consequently, the left pupil contracts less extensively to light and remains larger than the right one.

B and *C:* Similar calculations show the effect of the same lesion when the left eye (*B*) or the right eye (*C*) is stimulated by bright light, while the opposite eye remains in darkness.

than the normal pupil, but the symptom of alternation could not be produced. In an efferent lesion the same pupil always shows the damage, regardless of the side stimulated.

‡ References 4 and 5.

Since, therefore, neither the first afferent nor the efferent neuron can be responsible for the syndrome, the second neuron is left to be considered as the possible site of the lesion.

The possible effects resulting from lesions or groups of lesions within the second neuron will be illustrated by the diagrams and calculations in Figures 3 through 7. Although it is known that more visual fibers cross in the optic chiasm than remain uncrossed, in these calculations it is assumed that half of the pupillary fibers cross;

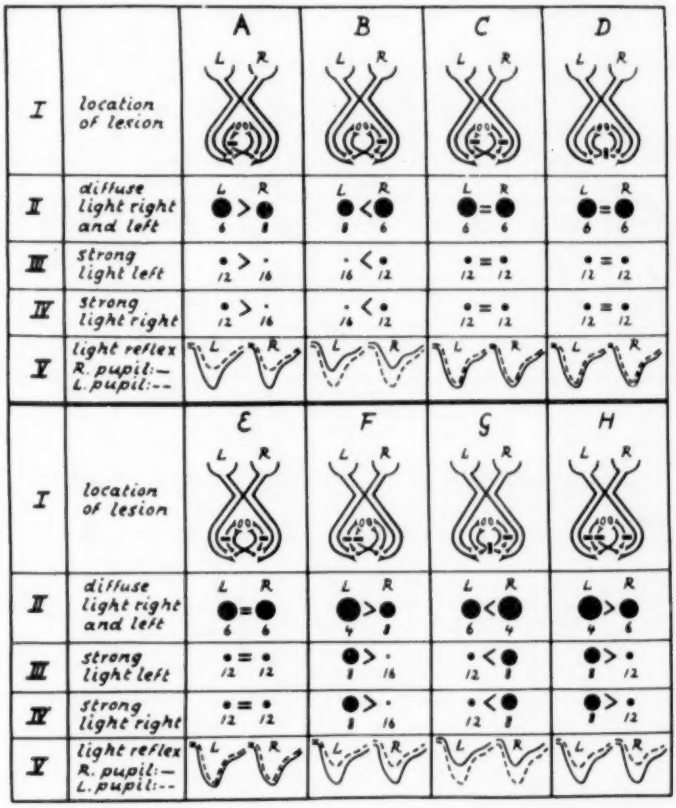

Fig. 4.—Effect of lesions or combinations of lesions limited to the second afferent neuron of the light reflex arc on the pupillary reaction to light.

I: Scheme of the first and second afferent neurons of the light reflex arc. Lesions are indicated by a square interruption of a path. An injured path is assumed to have lost one-half of its conductivity. These diagrams do not attempt to show the anatomical fiber arrangement.

II: Pupillary size when both eyes are illuminated by diffuse light of 4 f.-c. intensity per retinal half (cf. Fig. 3).

III and *IV*: Pupillary size when the left (*III*) or right (*IV*) eye is illuminated by strong light of 16 f.-c. intensity per retinal half, the opposite eye remaining in darkness.

V: Diagrams indicating the relation between direct and consensual reaction to light when the left (*L*) or the right (*R*) eye is stimulated. The solid line represents the right, the broken line the left, pupil. The absolute extent of the reflex in each case has not been considered in these diagrams.

the other half remain uncrossed, both in the optic chiasm and in the central decussation. The assumption of a 1 : 1 ratio of crossed and uncrossed pupillary fibers in each decussation is based on the following facts:

1. It is impossible to induce anisocoria by unilateral illumination in normal man, in contrast to lower mammals, such as cats, rabbits, or rats.[6]

2. In man, lesions limited to the optic nerve, optic chiasm, and optic tract do not cause anisocoria.[4]

Nevertheless, the possibility of unequal crossing of pupillary fibers in the optic chiasm, as it would affect these calculations, will be discussed below (page 755).

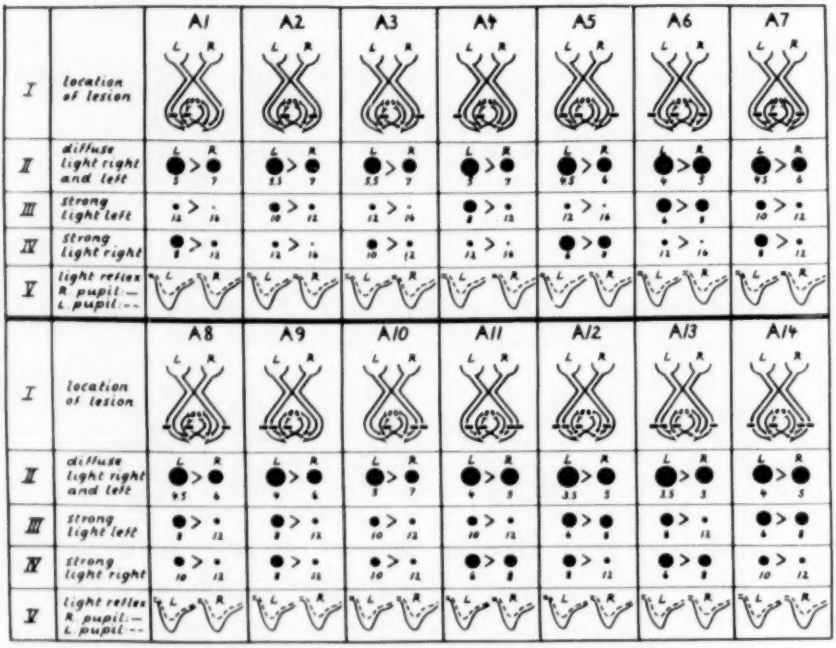

Fig. 5.—Effect of all combinations of first neuron lesions with the second neuron lesion *A* of Figure 4 on the pupillary reaction to light.

The same system of calculation and representation described in Figures 3 and 4 is used. It is seen that all possible combinations of optic lesions with the second neuron lesion *A* result in contraction anisocoria. However, none of these combinations results in the symptom of alternation. It is always the same pupil which shows the greater reaction; e. g., the right pupil always reacts more than the left one.

For greater ease in understanding, the calculations in Figures 3 to 8 are made with specific stimulation values. Diffuse, weak illumination of both eyes is assumed to equal 8 f.-c. intensity for each eye, i. e., 4 f.-c. for each retinal half. Strong light applied to the right or left eye, leaving the other eye in darkness, is assumed to equal 16 f.-c. per retinal half. A lesion, indicated on the diagrams as a square interruption of a path, is assumed to equal a 50% reduction in the conductibility of that path.

Figure 3 illustrates the use of this method of calculation. If, as given in Figure 3*A*, each retinal half receives a diffuse stimulation of 4 f.-c. intensity, then each pretectal area will receive a total stimulus value of 8. This stimulation value will be transmitted to the right pretectal area by the crossed optic fibers from the left

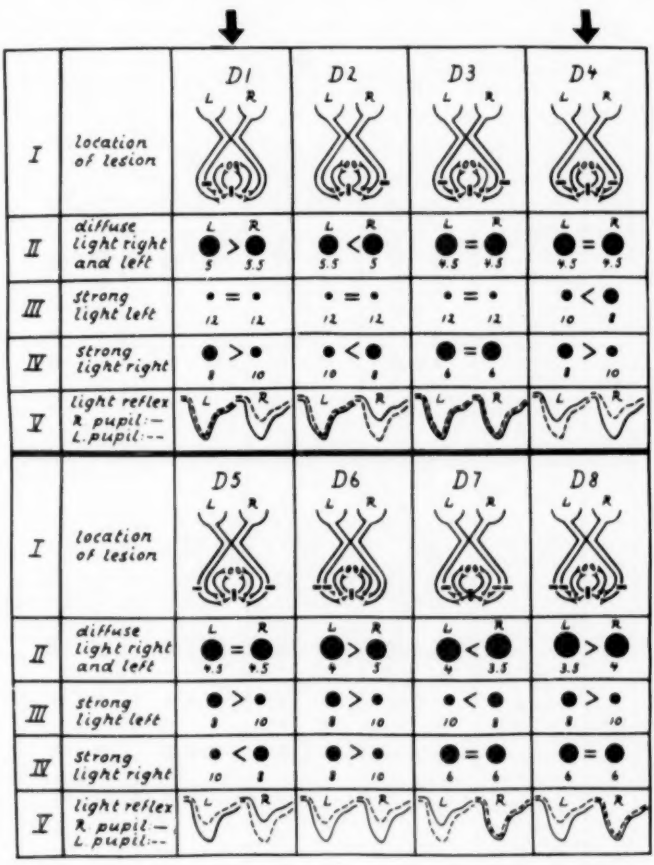

Fig. 6.—Effect of all combinations of first neuron lesions with the second neuron lesion *D* of Figure 4 on the pupillary reaction to light.

The same system of calculation and representation as in Figures 3, 4, and 5 is used.

D1 shows the unilateral type of alternating contraction anisocoria.

D2 and *D5* show alternating contraction anisocoria, but not the syndrome found in our clinical material, since the direct reactions on the stimulated side are less extensive than the simultaneous consensual reactions of the opposite pupil. In the clinical material, the direct reaction always exceeds the consensual reaction.

D3 shows no anisocoria.

D4 shows the bilateral type of alternating contraction anisocoria.

D6 shows contraction anisocoria, but not the alternating type.

D7 and *D8* show dynamic contraction anisocoria, but differ from the syndrome found in clinical cases. When the left eye is illuminated, the pupils become unequal, but the reaction of both pupils is less impaired than when the right eye is stimulated and the two pupils react equally. In the clinical material the opposite is true. The reactions are always more impaired when the eye is stimulated from which anisocoria is produced.

eye and the uncrossed fibers from the right eye, and will be transmitted to the left pretectal area by the crossed optic fibers from the right eye and the uncrossed fibers from the left eye. In the second neuron, half of the impulses will be transmitted by uncrossed fibers from each pretectal area to the third nerve nucleus on the same side, while the other half will cross through the posterior commissure to the third

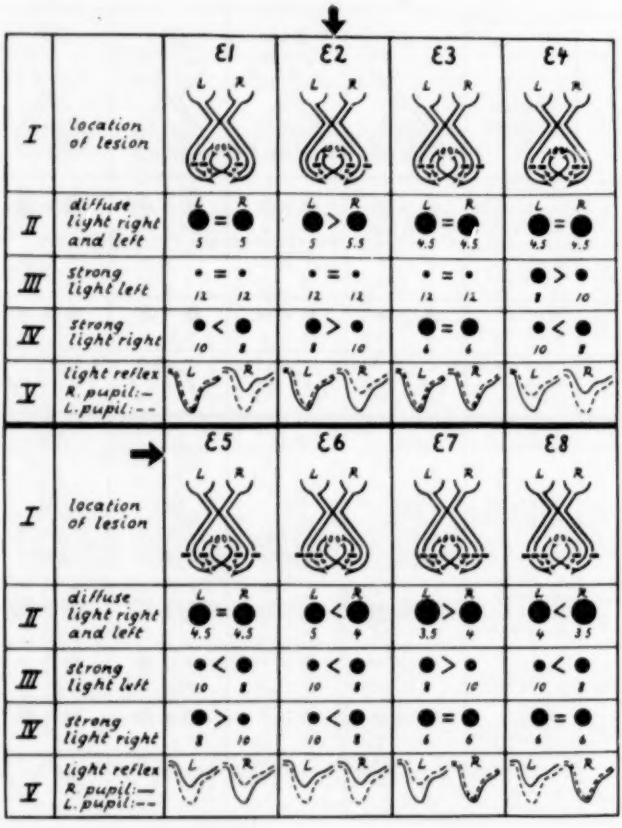

Fig. 7.—Effect of all combinations of first neuron lesions with the second neuron lesion *E* of Figure 4 on the pupillary reaction to light.

The same system of calculation and representation as in Figures 3 to 6 is used.

E1 and *E4* show alternating contraction anisocoria, but not the syndrome found in our clinical material, since the direct reactions of the stimulated side are less extensive than the consensual reaction of the opposite pupil. In the clinical material, the direct reaction always exceeds the consensual one.

E2 shows the unilateral type of alternating contraction anisocoria.

E3 shows no anisocoria.

E5 shows the bilateral type of alternating contraction anisocoria.

E6 shows no alternation, and the left pupil always reacts more extensively than the right one.

E7 and *E8* show alternating contraction anisocoria, but the reflexes are more extensive when the left (anisocoria) eye rather than the right (no anisocoria) eye is stimulated. In the clinical cases, the reactions are always more impaired when the eye from which anisocoria is produced is stimulated.

nerve nucleus on the opposite side. Normally, then, each third nerve nucleus would receive a total stimulation value of 8. But, since the crossed path from the right pretectal area to the left third nerve nucleus is damaged in the example in Figure 3, the left third nerve nucleus will receive a stimulation value of only 6. Consequently, the left pupil will be larger than the right one. The calculations for strong light stimulation of the right and of the left eye are shown in Figures 3 *B* and *C* respectively.

This same method is used for the calculations in Figures 4 to 7. The site of the assumed lesion or group of lesions is shown schematically at the head of each column (Line i). Below each of these diagrams are shown the calculated values for the left and right pupils when both eyes are stimulated by diffuse light (Line II) and when a strong light is applied to the left eye (Line III) or to the right eye

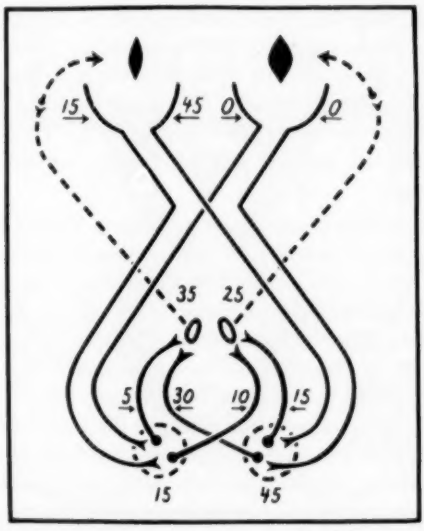

Fig. 8.—Physiological alternating contraction anisocoria in the cat, due to unequal fiber distribution in both the optic chiasm and the central decussation.

The method of calculation and representation is the same as in Figures 3 to 7. In the cat, more fibers cross than remain uncrossed in both commissures. It is assumed that three-fourths of the optic fibers cross in the optic chiasm to the pretectal area of the opposite side, and one-fourth remain uncrossed. In the central decussation two-thirds of the fibers cross; one-third remain uncrossed. These numerical values are assumed on the basis of experiments on cats, but are probably only approximately correct. However, use of different numbers does not change the relation between directly and consensually reacting pupils. The direct reaction always exceeds the consensual one.

(Line IV). Line V shows a schematic graph of the relationship between the direct and the consensual reflex to light when the left (L) or the right (R) eye is stimulated. The solid line always represents the right pupil, the broken line the left pupil. It should be noted that the diagrams of the pupillary pathways in Figures 3 to 7 (Line I) are schematic representations and are not topographically exact and that in the graphs of the relationship between direct and consensual reactions to light (Line V) the absolute extent of the reflex has been disregarded.

Figure 4 shows that no lesion or combination of lesions limited to the second neuron could cause alternating contraction anisocoria. In Figure 4 *C*, *D*, and *E*, no anisocoria is found. In the remaining cases (Fig. 4 *A*, *B*, *F*, *G*, and *H*) contraction anisocoria appears, but the symptom of alternation is absent. The relative sizes of the right and left pupils do not change regardless of the side stimulated. In Figure 4 *A*, for example, the left pupil is always the larger one, whether both eyes (Line II), the left eye (Line III), or the right eye (Line IV) is stimulated.

It is therefore seen that neither the first or the second neuron nor the efferent neurons alone can be the site of the lesion causing alternating contraction anisocoria. How, then, can this syndrome be explained?

Nature itself points to a possible explanation. In normal cats bilateral alternating contraction anisocoria is regularly found. In these animals the crossed fibers, both in the optic chiasm and in the central decussation, greatly outnumber the uncrossed fibers (Fig. 8). Consequently, upon unilateral illumination of, for example, the left eye, more optic impulses reach the right pretectal area than remain on the same side to reach the left pretectal area. Furthermore, in the second neuron more impulses cross from each pretectal area to the opposite third nerve nucleus than remain uncrossed. Therefore, since the right pretectal area receives more optic impulses than does the left one, the left third nerve nucleus is more intensively stimulated than the right.

This phenomenon in cats points to the possibility that in man alternating contraction anisocoria might be caused by a combination of one or more lesions of the second neuron with one or more lesions of the first neuron. In order to consider all the theoretical possibilities, we combined each of the second neuron lesions (Fig. 4 *A* to *H*) with all possible lesions, or groups of lesions, within the first neuron. As an example, in Figure 5, the second neuron lesion *A* is combined with all possible first neuron lesions. All these combinations result in contraction anisocoria, which differs in each case as to the extent of the total reflex and the variations in the relationship between the direct and the consensual reactions. Since the right pupil always becomes smaller than the left one, none of these combinations of lesions results in the symptom of alternation. Similar results are found in Series *B*, *F*, *G*, and *H*, while no anisocoria is seen in Series *C*; they are therefore not shown here. Only Series *D* (Fig. 6) and *E* (Fig. 7) show the alternation phenomenon. They will be discussed in more detail.

Of all the possible combinations contained in the two series, only *D1* and *E2* show the unilateral syndrome and *D4* and *E5* the bilateral syndrome as it is found in our clinical material. *D2*, *D5*, *D8*, *E1*, *E4*, and *E7* show the alternation phenomenon, but in them the consensual reaction exceeds the direct reaction in extent. This condition was not seen among our cases of alternating contraction anisocoria, in which we always found the direct reaction to exceed the consensual one. *D3* and *E3* show no anisocoria at all, while *D6* and *E6* show contraction anisocoria but not of the alternating type. *D7*, *D8*, *E7*, and *E8* show a unilateral type of alternating contraction anisocoria, but it differs from that in our clinical cases in that the light reflexes are less extensive when the pupils respond equally (Figs. 6 *III* and 7 *III*) than when they respond unequally (Figs. 6 *II* and 7 *II*). In our clinical material the opposite is true; i. e., whenever the total extent of the light reflex is visibly

diminished, it is less extensive upon stimulation of the eye which produces anisocoria than upon stimulation of the eye which produces symmetrical pupils.

Of the 100 theoretically possible combinations of first neuron and second neuron lesions, we therefore find only two (*D1* and *E2*) which could result in the unilateral syndrome and a second pair (*D4* and *E5*) which could give the bilateral syndrome of alternating contraction anisocoria. The probability of the lesions being located according to the *D* series *vs.* a location according to the *E* series will now be discussed.

Both series have in common that two symmetrical second neuron paths are damaged; in the *D* series only crossed fibers and in the *E* series only uncrossed fibers are assumed to be involved. *D1* and *E2* show damage to a single first neuron path, and *D4* and *E5* show damage to two symmetrically placed first neuron paths.

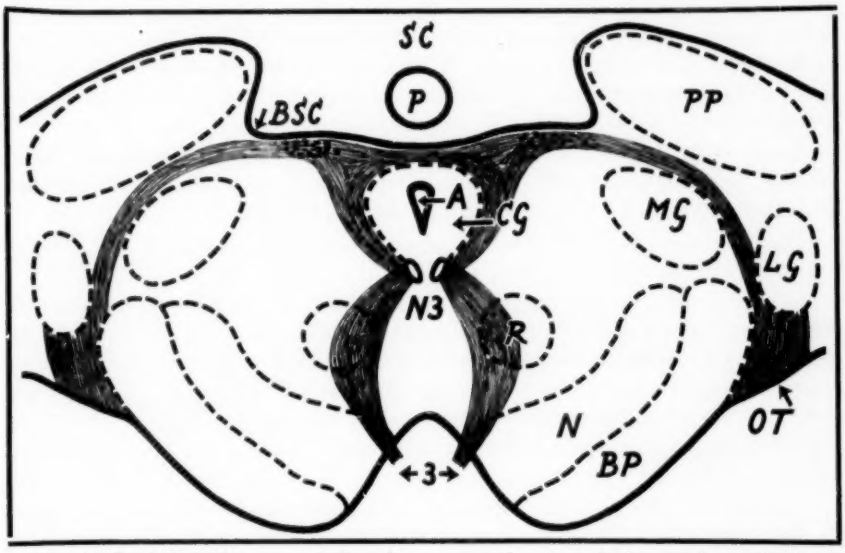

Fig. 9.—Semischematic representation of a cross section through the anterior midbrain. *A* indicates aqueduct of Sylvius; *BP*, basis pedunculi; *BSC*, brachium of the superior colliculus; *CG*, central gray matter; *LG*, lateral geniculate body; *MG*, medial geniculate body; N, substantia nigra; *OT*, optic tract; *P*, pineal body; *PA*, pretectal area; *PP*, posterior pulvinar; *R*, nucleus ruber; *SC*, superior cistern; *3*, third nerves.

Here, also, is the *D* series only crossed and in the *E* series only uncrossed fibers are involved.

Assumption of selective damage to either all crossed or all uncrossed fibers in the first neuron presents no great difficulty, since it is likely that the pupillary fibers, upon emerging from the highly ordered system of the optic tracts, would remain ordered as they pass through the brachia of the superior colliculi to the pretectal areas. Microscopic observations seem to support this assumption, since no considerable intermingling of fibers is evident.

As to the second neuron, one might be inclined to favor the *E* series from a phylogenetic point of view. The uncrossed fibers are phylogenetically the more recent ones, not yet fully developed even in the cat. It is tempting to ascribe to them a greater vulnerability. However, the topographical arrangement (Fig. 9) of the

second neuron would make it necessary to assume two small, discrete, symmetrically placed lesions in order to damage the uncrossed fibers while sparing the crossed fibers. The frequent occurrence of the syndrome makes such an explanation unlikely. In contrast, it can easily be imagined that a relatively inextensive pathological process would affect only the right and left crossed second neuron fibers as they pass, closely intermingled, through the posterior commissure. Such a location of a superficial lesion is very probable, since only the delicate ependymal layer separates the fibers from the spinal fluid amassed in the superior cistern above them (Fig. 9).

We conclude that anatomical and physiological reasons make the explanation according to Figure 6 *D1* and *D4* most likely. *D1* would cause the unilateral syndrome, *D4* the bilateral. A pathological process, transferred by the spinal fluid aggregated in the cistern directly above, would injure the exposed pupillary fiber tracts running through this small area. Damage to the posterior commissure would involve the crossed fibers from the right and left pretectal areas. The crossed first neuron fibers could be harmed as they pass through the brachia of the superior colliculi, whereby damage to one brachium would cause the unilateral syndrome, and damage to both brachia the bilateral syndrome.

An infection may, of course, also be transmitted by way of the blood vessels. Further, tumors in this region, for instance, pineal body tumors, could exert pressure on these exposed paths, resulting in similar symptoms.

Possible objections which could be raised against these conclusions are mainly concerned with the following points of view:

I. It could be assumed that a point-by-point order of pupillary fibers would be preserved across the synapse of the pretectal area up to the third nerve nucleus in such a way that the fibers which cross in the optic chiasm synapse with second neuron fibers crossing back in the posterior commissure, while the uncrossed optic impulses remain uncrossed in the second neuron also. If this assumption were correct, a single first neuron lesion would suffice to explain the syndrome of alternating contraction anisocoria.

This assumption is at variance with pupillographically established facts: (1) Clinical cases with lesions limited to the first neuron consistently failed to show anisocoria, and (2) it can be shown in cats that it is unimportant for the distribution of impulses in the second neuron whether the optic impulses impinging on the pretectal area are transmitted by crossed fibers from the opposite retina or by uncrossed fibers from the homolateral eye. This fact is demonstrated by the following experiments.

(*a*) When in a cat the left optic nerve and the right optic tract were severed, the right pretectal area was cut off from afferent stimulation and the left pretectal area could be stimulated only by crossed optic fibers from the right eye. After the animal had recovered from the operation, light reflexes were elicited from the right eye. Both pupils contracted, the right more than the left. This experiment showed that the greater portion of impulses traveling over the crossed optic fibers from the right eye cross back in the posterior commissure, but some of the impulses remain uncrossed.

(*b*) When in another cat the right optic nerve and right optic tract were cut, the right pretectal area, again, no longer received afferent stimuli. The left pretectal

area received only uncrossed fibers from the left retina. When this animal's left eye was stimulated by light, the right pupil, which now reacted consensually, again became smaller than the left pupil, which was directly stimulated. This experiment proved that the uncrossed impulses from the left retina are distributed by the left pretectal area in the same manner as the crossed impulses from the right retina, whereby the major portion of the impulses reaches the third nerve nucleus opposite the stimulated pretectal area and a smaller part remain uncrossed.

Therefore, it can be concluded that a new distribution of impulses is effected in the second neuron and that the point-by-point order of the first neuron is lost in this synapse.

II. It can further be objected that, in analogy with the visual fibers, more retinal pupillary fibers cross in the optic chiasm than remain uncrossed (cf. above, page

TABLE 2.—*Clinical Conditions Associated with Alternating Contraction Anisocoria*

Disease	Type of Alternating Contraction Anisocoria: Unilateral Uncomplicated	Unilateral Complicated	Bilateral Uncomplicated	Bilateral Complicated	Total	Percentage
Nonspecific infections	9	16	6	4	35	23.3
Syphilis	..	11	2	4	18	12
Multiple sclerosis	3	9	1	3	16	10.6
Arteriosclerosis	..	8	1	1	10	6.7
Posteoncussion syndrome	4	4	3	1	12	8
Hypertension	1	7	..	4	15	10
Diabetes	1	2	..	..		
Hyperthyroidism	..	2	1	1	4	2.7
Psychopathies and neuroses	6	11	1	1	19	12.7
Heredodegenerative conditions	5	9	4	3	21	14
Totals	29	79	20	22	150	100
	108		42			

748). If this assumption were true, a lesion limited to the second neuron would suffice to cause alternating contraction anisocoria.

The calculations of Figures 3 to 7 show that—a physiological symmetric weakness of the uncrossed retinal fibers being assumed—the second neuron lesions *D* and *E* alone would result in alternating contraction anisocoria. The lesion *E* would necessitate two small discrete and symmetrically arranged foci. We have already discussed (cf. pages 753, 754) the relative improbability of this lesion as compared with the second neuron lesion *D*.

III. If, as Behr § believed, both the first and the second neuron fibers were unevenly distributed with more crossed than uncrossed fibers, it should be possible to elicit alternating contraction anisocoria symmetrically from each eye in normal man. We have repeatedly shown that this is not the case (cf. page 748). In pathological cases, the syndrome of alternating contraction anisocoria is often bilateral but seldom symmetric.

§ References 7 and 8.

CLINICAL CONSIDERATIONS

The localization, as described above, of alternating contraction anisocoria is further supported by the clinical nature of the cases in which the syndrome occurs.

In 35% of the cases the syndrome is due to infections which are probably transmitted by the cerebrospinal fluid. There may be a special accumulation of the noxious agent in the superior cistern immediately above the supposed site of the damage. If Marburg [9] and many others are right in that multiple sclerosis is disseminated in the central nervous system by way of the cerebrospinal fluid or the blood vessels and is due to a virus infection, 11% more, i. e., 46%, of our cases can be attributed to virus infection. Neuroses and psychopathies are not supposed, by their very nature, to be concerned with the development of organic central nervous symptoms, such as alternating contraction anisocoria. If such symptoms are, nevertheless, present within these diseases, as in 12% of our material, it must be concluded that complicating inflammatory, degenerative, or arteriosclerotic processes must have been the cause. The same is probably true in cases of hypertension and diabetes, in which local vascular pathology may be the immediate cause of alternating contraction anisocoria. In the cases of hyperthyroidism toxemic influences are the possible cause.

Among the infectious causes of alternating contraction anisocoria, acute virus infections play a particular role because they frequently occur within clinical pictures in which they are tied to certain other nervous symptoms. These conditions, because of their clinical importance, will be described in a subsequent publication.‖

SUMMARY AND CONCLUSIONS

A pupillary syndrome of alternating contraction anisocoria is described. In the unilateral syndrome, the pupils remain equal during light stimulation of one eye but they become unequal when the other eye is illuminated. In the bilateral syndrome, anisocoria results from light stimulation of either eye. The directly stimulated eye always shows the smaller pupil. Bilateral alternating contraction anisocoria is rarely symmetrical and is usually more pronounced on stimulation of one eye than on stimulation of the other. The syndrome is frequently complicated by additional pupillary pathology.

The syndrome is probably caused by a combination of lesions in the first afferent neuron (from retina to the pretectal area) and the second afferent neuron (from the pretectal area to the third nerve nucleus) of the light reflex arc.

The theoretically possible combinations of lesions of the first and second afferent neurons of the light reflex pathway were tabulated. Of the 100 combinations, only 2 were found which would result in the unilateral syndrome and a second pair which would lead to the bilateral syndrome as they appear in the clinical material. The probability of one or the other of these possible localizations is discussed.

It is concluded that the lesion is probably located in the posterior commissure and in one (unilateral syndrome) or both (bilateral syndrome) brachia of the superior colliculi. It involves crossed fibers of both the first and the second neuron of the light reflex arc and is probably situated beneath the superior cistern.

Although the syndrome may be caused by all types of pathological processes in this region, it is found most frequently in cases of specific and nonspecific infections of the central nervous system (35%), multiple sclerosis (11%), vascular pathology (17%), and heredodegenerative conditions (14%).

‖ Reference 10.

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NEUROMYELITIS OPTICA SIMULATING SPINAL CORD TUMOR

Report of a Case, with a Review of Nine Additional Cases

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THE CLINICAL features of neuromyelitis optica are generally regarded by clinicians as distinct and unique in character, usually permitting prompt recognition, but in some cases the diagnosis may be difficult. When attended by pronounced visual disturbances, acute or subacute spinal cord syndromes should arouse suspicion of neuromyelitis optica. Occasionally, however, the onset of optic neuritis may be delayed for weeks or months, thus allowing some confusion in the clinical picture. On the other hand, optic neuritis may precede myelitis for considerable periods of time, again leading to diagnostic difficulty. In the latter instance, if rapidly failing vision and minimal papilledema are the only findings, the diagnosis of intracranial tumor may be excluded only after ventriculography. However, as far as we know, the first of the following cases is the only reported instance in which neuromyelitis optica so closely resembled spinal cord tumor that laminectomy was actually performed.

REPORT OF CASES

CASE 1 (J. H. H. #572470).—A 29-year-old farmer was admitted May 17, 1951. He had been in good health until three days before admission, when he noted aching pains in both thighs. Weakness of the right arm and leg and loss of temperature sensation on the left side of the body developed the following day. Neurological examination at that time revealed minimal pyramidal tract signs on the right and a sensory level at C6 on the left. Cervical and thoracic spine x-rays were normal. A myelogram was obtained on May 21, and this revealed a complete block at the level of C6. A cervicodorsal laminectomy was done on May 23 by one of us (F. J. O.). The spinal cord appeared swollen, but no tumor was seen. After an initial improvement during the first few postoperative weeks, the patient had a relapse, with rapidly progressing paraplegia, bladder difficulty, and sensory loss bilaterally below T6. During the month of July steady improvement took place, so that by the time of discharge, on Aug. 1, he could walk without assistance. Sensation returned to normal except for a small area over the medial aspect of the left calf. During the first two weeks at home, in August, improvement continued, but in the latter part of the same month rapidly progressing paraplegia developed, with numbness below the umbilicus and loss of bladder and bowel control. During the three days prior to his readmission, on Sept. 1, he noted marked blurring of vision in both eyes, accompanied by a dull headache.

Neurological examination on readmission, on Sept. 1, revealed bilateral papilledema, slightly more pronounced on the right. There were no hemorrhages, but the optic nerve heads were definitely swollen and blurred. There was a large central scotoma bilaterally, and the visual acuity was 20/200 R. E. and 20/100 L. E. The pupils were large and equal and reacted poorly. There was complete flaccid motor paralysis below T6 and complete loss of sensation below T3

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on the right and T4 on the left, with loss of sphincter control. The tendon reflexes were increased in the left upper limb and decreased in both lower limbs, those on the right being less active than those on the left. The plantar response was extensor bilaterally, but there was no ankle clonus.

After a month of symptomatic treatment in the hospital the patient was discharged, unimproved. During the next six months some strength returned in the lower limbs, and he was able to get about in a walker. Bowel function was managed successfully by a daily morning enema. Although bladder function did not improve, a penile clamp proved quite satisfactory. In August, 1952, he was readmitted because of urinary tract infection and bladder calculi. Neurological examination at this time revealed that the optic discs were very pale, but he could read large newspaper type. Both legs were markedly wasted and spastic, with hyperreflexia and ankle clonus. There was slight hypesthesia and hypalgesia below the level of T8 on both sides. When last seen, in January, 1954, vision was 20/100 in both eyes. The patient was spastic but could walk.

Comment.—In reviewing the sequence of events in this case, it is evident that the rapid onset of spinal cord signs was more suggestive of inflammatory or infectious process than of spinal cord tumor. However, considering the presence of a complete block on myelography at the expected neurological level, it seemed reasonable that the lesion was due to hemorrhage associated with a neoplasm and, therefore, that laminectomy was indicated. The operative findings, as well as the subsequent developments, afforded no reliable clues to the etiology until the onset of optic neuritis accompanied by exacerbation of myelitis, three months after the initial symptoms.

It seems reasonable to explain the subarachnoid block on myelography on the basis of swelling of the cord due to an intense myelitic process. In reviewing the previously reported cases of neuromyelitis optica, we have found only one other case in which myelography revealed complete subarachnoid obstruction. Silbermann,[3] in 1945, reported a case of neuromyelitis optica in which cisternal injection of iodized oil (Lipiodol) revealed a block at C6, with the lower level at L2, as determined by lumbar injection of iodized oil. Laminectomy was not performed, however. In 1952 McIntyre [2] described a case of neuromyelitis optica with xanthochromia and complete block, as demonstrated by manometric test, but surgical exploration was not done. McIntyre,[1] in 1942, reported a case alleged to have been neuromyelitis optica in which laminectomy was done two years after a negative hypophyseal exploration, but the history and operative findings were those of chronic cystic arachnoiditis, and not in keeping with neuromyelitis optica.

Review of Previous Cases.—In reviewing the files of The Johns Hopkins Hospital between 1925 and 1952, a total of 10 cases of neuromyelitis optica were found. In all of these, both myelitis and optic neuritis were present at some time. In addition, there were seven cases in which the diagnosis of neuromyelitis optica was made in the absence of myelitis. In this group, the chief clinical features were sudden or rapid onset of visual failure in one eye, followed by the involvement of the other eye within a few weeks, without objective signs of spinal cord disease. Although some clinicians believe that such cases represent abortive forms of neuromyelitis optica,[5] it seems that myelitis and optic neuritis must be present to justify this diagnosis and must have their onset within a relatively brief period of time. Of the 10 cases reviewed, 8 were females and 2 were males. The average age at the time of onset of the first symptoms was 27.5 years. In previously reported cases there has been

considerable difference of opinion as to whether myelitis or optic neuritis is the first to appear. In the 10 cases we have studied myelitis occurred before the optic neuritis in 5 cases, while the reverse was true in 4 cases. In one case the onset of the two was simultaneous. The interval between the appearance of myelitis and that of optic neuritis varied from simultaneous onset to one year, with the largest percentage less than six weeks. The average interval was three months. It is interesting that in the cases in which definite sensory levels were elicited there was a marked predilection for the thoracic segments.

The following are the summaries of the additional nine cases reviewed from the files of The Johns Hopkins Hospital.

Case 2 (J. H. H. #565710).—A 25-year-old white woman was admitted in February, 1951. She had had rapid spontaneous onset of paralysis of both legs, with marked improvement within a few hours, followed by return of symptoms the same evening. Rapid recovery followed, but two weeks later paraparesis returned, accompanied by headache, marked loss of vision, paresthesias in the hands, and low backache. Neurological examination revealed bilateral papilledema, tenderness of the globes, and marked central scotomata, with reduction of visual acuity to 4/200 left and 5/200 right. Marked paraparesis, more pronounced on the right, hyperreflexia on the right, and hyperesthesia of the right side of the body. The leucocyte count was 17,000 per cubic millimeter. Serology negative. X-rays of the skull, spine, and chest were negative. EEG was normal. Lumbar puncture revealed a pressure of 140 mm. of water, total protein 83 mg. per 100 cc., and colloidal gold reaction 1110000000.

Comment.—In this case symptoms of myelitis followed an irregular course and preceded optic neuritis by two weeks. Unfortunately, the subsequent course of this case is not known.

Case 3 (J. H. H. #446085).—A 52-year-old white woman was admitted May, 1948. She had had rapid decrease of vision seven months previous to admission and gradually increasing ataxia, beginning one week after visual symptoms. She was bedridden for one week before admission. Neurological examination revealed pallor of the optic discs with bilateral central scotoma, spastic paraplegia in adduction, and marked loss of sensation below the sixth thoracic dermatome. The plantar response was extensor bilaterally. Visual acuity: right eye 3/200; left eye 1/200. Lumbar puncture revealed a pressure of 95 mm. of water; clear and colorless fluid, containing 92 mg. of total protein per 100 cc., negative serology, and colloidal gold reaction of 3322100000. Cystometrogram was normal. The patient was transferred to a nursing home for terminal care.

Comment.—Although the onset of myelitis in this case was gradual, when contrasted with the characteristically rapid type, its time relationship to the visual symptoms establishes the nature of neuromyelitis optica. A similar clinical picture may be encountered in multiple sclerosis, but many of the important findings of the latter were lacking.

Case 4 (J. H. H. #349164).—A 16-year-old white girl was admitted in April, 1945. She had transient diplopia for six weeks, with blurring of vision at night. Eight days after a mild "head cold" with postnasal drip, she noted paresthesias in the lower limbs. Within a few hours headache developed, as well as paresthesias in the upper limbs and marked weakness of the legs. Fever, vomiting, urinary incontinence, and constipation were also present. Neurological examination revealed almost complete flaccid paraplegia below the hips. There was hypalgesia over the abdomen and lower limbs, and areflexia in the legs; plantar reflexes, flexor. Temperature was 102 F.; white blood cells 11,700 per cubic millimeter. Lumbar puncture revealed pressure of 100 mm. of water; clear and colorless fluid, containing 6 white blood cells per cubic millimeter and 11 mg. of total protein per 100 cc., and negative culture. Gradual improvement was not related to penicillin and sulfadiazine treatment. One year later the patient had pain in both eyes, followed by slight return of weakness of legs, with remission of both symptoms.

Comment.—The severity of visual symptoms varies, as do the spinal cord symptoms. Either may predominate while one is minimal. In this case, visual symptoms were slight or abortive and could have been unrecognized. Characteristically, however, the visual symptoms are more pronounced than illustrated in this case.

CASE 5 (J. H. H. #241497).—A 37-year-old white woman was admitted in September, 1941. She had had a rapid loss of superficial and temperature sensation in the right lower extremity 15 months previously, followed by rapid improvement. One month later there was rapid loss of central vision in the right eye, followed a few days later by rapidly failing vision in the left eye. A month later pains developed in the right leg. Rapidly progressing weakness of both legs followed, and complete paraplegia supervened, with loss of vesical and rectal sphincters. Little improvement occurred. Examination one year after onset of paraplegia revealed visual acuity in the right eye limited to light perception only; left eye blind. Both pupils were dilated, with loss of light response on the left and minimal reaction to light on the right. Both discs were extremely pale. There were flexion contractures at the right hip and knee, paraplegia, hyperreflexia of lower limbs, and ankle clonus. Sensation was totally lost below T6 dermatome. Lumbar puncture revealed no block and a pressure of 140 mm. of water. The spinal fluid was clear and colorless, with 1 white blood cell per cubic millimeter, total protein content of 25 mg. per 100 cc., colloidal gold curve 000000000, and negative Wassermann test.

Comment.—This case represents neuromyelitis in a severe form. The majority of cases improve in varying degree after the first episode, although subsequent attacks result in progressive neurological deficit as a general rule.

CASE 6 (J. H. H. #205268).—A 47-year-old white man was admitted in July, 1940. Six years previously he had had an attack of pleurisy, and three years later a lung abscess developed. There was apparent recovery from both illnesses. Two months before admission there was rapid loss of vision in the left eye, proceeding to blindness within one week. Three weeks later vision diminished rapidly in the right eye. Examination at the Wilmer Ophthalmological Institute two months after the onset of symptoms in the left eye revealed visual acuity in the right eye limited to counting fingers at a distance of 4 ft. (120 cm.); left eye was blind to light. Right pupil reacted minimally; left pupil was fixed; both were dilated. There was marked temporal pallor of the right disc, blurring of the nasal border, and a small area of chorioretinitis in the inferior temporal quadrant. The left disc presented a similar picture. The tendon reflexes were decreased in the left upper limb and in both lower limbs. There was atrophy of the left quadriceps, hamstrings, and glutei, with corresponding weakness. Sensory examination revealed hypalgesia in the right leg.

X-rays of the skull, cervical spine, and optic foramina were normal. Chest x-rays revealed minimal infiltration of the right apex, not characteristic of tuberculosis. Lumbar punctures revealed normal pressure. Spinal fluid cell count 0; total protein 75 mg. per 100 cc., colloidal gold curve 2321000000, and Wassermann reaction negative.

Four months later the patient died at home. Although autopsy was not obtained, his family physician wrote that there had been "rapid deterioration of health" and loss of use of the lower extremities.

CASE 7 (J. H. H. #79864).—A 9-year-old white girl was admitted in September, 1932. There was nausea, vomiting, anorexia, and jaundice of two days' duration, followed one week later by rapidly failing vision. She had progressive paralysis of the lower limbs, beginning in the left foot and two days later proceeding to the right foot, leading to paraplegia and sphincter decontrol and involving the upper limbs to less degree. Neurological examination revealed pallor and blurring of the optic discs. Visual acuity was reduced to light perception only. Flaccid paraparesis, with slight weakness of upper limbs. Loss of superficial sensation below the umbilicus. Hyporeflexia in the lower limbs. Lumbar puncture revealed a pressure of 80 mm. of water, 60 white blood cells (80% monocytes, 20% polymorphonuclear leucocytes), no block. Cerebrospinal fluid culture was negative. Signs of ascending spinal cord involvement appeared, and the patient died with bulbar paralysis 34 days after admission. Autopsy revealed extensive involvement of the spinal cord, more marked caudally, where the cord was liquefied. Rostrally the cord contained

numerous cavitations and marked demyelination. The optic chiasm and nerves and cerebral hemispheres (especially the occipital lobes) were extensively involved. (This case has been reported previously in detail by Walsh,[4] Case 1.)

Comment.—The relationship to the gastrointestinal symptoms is not clear, but a toxi-infectious etiology is suggested. Pleocytosis of this degree is unusual in neuromyelitis optica. Poliomyelitis is excluded by the prominent sensory loss and visual impairment, and the autopsy findings were characteristic of neuromyelitis optica.

Case 8 (J. H. H. #71053).—A 36-year-old white woman was admitted in July, 1937. She had had severe abdominal pains and progressive weakness of the legs, within a few days accompanied by pains in the lower extremities and slight fever. Shadows noted before her eyes, and within a few days loss of the lower half of vision in each eye, then total blindness, occurred. Neurological examination 15 months later revealed pallor of the discs and vision limited to light perception. Paraplegia in adduction, weakness of the hands, rectal and vesical paralysis. Loss of superficial sensation below T7 dermatome bilaterally. Decreased tendon reflexes; extensor plantar responses. Within three years vision had returned to "almost normal," but no improvement in cord symptoms was noted.

Comment.—This case illustrates neuromyelitis in its complete form. Unfortunately, severe spinal cord symptoms do not subside as completely or as frequently as severe visual symptoms. Fever accompanying the onset suggests a toxi-infective etiology in some cases, but in the majority no febrile phases appear.

Case 9 (J. H. H. #74271 [U-38045]).—A white girl, age 9 years, was admitted July 10, 1931. Five months previously she had developed transverse myelitis in the midthoracic region over a period of four weeks. This attack had been preceded by an upper respiratory infection. After an incomplete recovery from the paraparesis, a relapse occurred one month later, with partial bulbar palsy. Nine months later she was able to return to school and climb stairs alone. Twelve months after the onset of her illness she developed rapid loss of vision in the right eye, with a large central scotoma and papilledema of 3 D. Vision at that time was ½/200 R. E., 20/15 L. E. After 17 months visual acuity was 20/15 bilaterally. (This case has been reported previously in detail by Walsh,[4] Case 2.)

Comment.—The occurrence of two episodes of myelitis and subsequent optic neuritis justifies the diagnosis of neuromyelitis optica. An interval of 12 months between the onset of spinal cord involvement and that of optic neuritis is unusually long.

Case 10 (J. H. H. #U-16395).—A white girl, age 17 years, was admitted in January, 1928. She had developed rapid loss of vision in both eyes, with one day's interval between the times of onset, two weeks previously. Neurological examination revealed only anisocoria with optic atrophy, more pronounced on the right. Visual acuity was 3/200 R. E., 6/200 L. E. During the next eight days she became blind in the left eye. A left frontal craniotomy was done and the chiasmal region explored, but no tumor was found. During this procedure the left optic nerve was divided. Three weeks postoperatively, during an uneventful recovery, she developed ankle clonus, which lasted for one month. Vision returned to 15/100 during the next three weeks, but four months later partial paraplegia developed. After partial recovery, complete blindness in the right eye developed seven months later. Vision returned to 10/100 in the right eye during the next six months. In February, 1933, five years after the onset of her first symptoms, she had her third attack of myelitis, with spastic paraplegia, urinary retention, a sensory level at T3, and a Horner syndrome on the left. The last follow-up examination, six months later, revealed visual acuity of 15/100 in the right eye and marked residuals of transverse myelitis. (This case has been reported previously by Walsh,[4] Case 3.)

Comment.—This case was an unusual one, in that there were three attacks of myelitis and two attacks of optic neuritis. The onset of her disease was such that a chiasmal tumor was suspected and an exploratory operation performed.

GENERAL COMMENT

That neuromyelitis optica is a rare disease is evident by the fact that only 10 cases could be found in the files of The Johns Hopkins Hospital during the 27-year-period from 1925 to 1952. The diagnosis is usually difficult and may be confused with brain tumor or spinal cord tumor. There appears to be no preference for neuritis or myelitis to develop first. The interval between the times of onset is usually less than 6 weeks but may be as long as 12 months. In this series the sex ratio was 4:1, with females predominating. Involvement of thoracic segments is the rule, with both motor and sensory findings.

The diagnosis often cannot be made until long after the first symptoms appear. If myelitis occurs first, intraspinal neoplasm can usually be excluded by the rapid onset, but rarely myelography may be necessary. Poliomyelitis can be dismissed from consideration in most cases because of the marked sensory disturbances, the transverse type of lesion, and pyramidal tract signs. When papilledema accompanies optic neuritis, intracranial tumor may be excluded by the marked visual loss, out of proportion to the papilledema, but rarely ventriculography may be required. In most cases the rapid onset of transverse myelitis would be indicative of neuromyelitis optica, but in the first case unilateral symptoms predominated initially. In such an instance myelography may be justified to exclude vascular tumors of the cord.

SUMMARY

A case of neuromyelitis optica in a 29-year-old farmer is described in which a complete block was demonstrated at the level of C6 on myelography and laminectomy was performed. The true diagnosis was not established until three months later, when an exacerbation of myelitis occurred, accompanied by optic neuritis. Nine additional cases of neuromyelitis optica were reviewed from the files of The Johns Hopkins Hospital between the years 1925 and 1952.

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STUDIES ON THE CENTRAL EXCITATORY STATE

I. Factors Responsible for the Variability of the Motor Response to Cutaneous Stimulation in Human Subjects with Isolated Spinal Cords

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SIR CHARLES SHERRINGTON, in 1903, during his investigation of the "scratch" reflex in dogs with transected spinal cords, used a heat lamp as a source of noxious stimuli.[1] He observed that thermal radiation "applied locally to the skin of the reflexogenous zone suffices, if not merely 'warm' but 'hot' [to the hand], to at once provoke the scratch reflex." He also observed that a heated metal plate evoked the scratch reflex in the spinal dog only after it had reached the temperature of "85 C. or more." It was observed subsequently by other investigators that immersing the feet of paraplegic patients in ice water or hot water could evoke withdrawal movements but that these responses were variable and unpredictable.* However, the stimulus intensities required to evoke reflex withdrawal in animals and humans with transected spinal cords have not been adequately measured. Therefore, quantitated thermal stimuli were applied to the extremities of paraplegic patients. The purpose of these investigations has been to ascertain the intensity of thermal stimulation that would evoke reflex movements in human subjects with isolated spinal cords, and to define the factors responsible for the variability of the threshold for these responses. From these observations inferences concerning the central excitatory state have been made.

MATERIAL

Subjects.—The 20 subjects were paraplegic males ranging from 20 to 59 years of age. Two of them had had spinal cord tumors; 11 had had gunshot injuries of the spine, and 7 had had trauma sustained in swimming and automobile accidents (Table). These subjects had transverse spinal cord lesions at levels from C5 to T9, with, in all probability, complete transection, as evidenced by absence of sensation and voluntary movement below the level of the lesion, sexual impotence, and loss of bladder and bowel control. The lower extremities

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From the New York Hospital-Cornell Medical Center, the Departments of Medicine (Neurology) and Psychiatry, and the Veterans Administration Hospital, Bronx, Department of Neuropsychiatry.

* References 2 and 3.

exhibited involuntary movements which sometimes occurred spontaneously but which always occurred when the sole of the foot was repeatedly pricked with a pin. The paraplegic state had existed in each patient for six months or more, and recovery from the initial spinal shock had occurred. Classification as to age, and as to site and type of lesion, is recorded in the accompanying Table.

Summary of Data Obtained in Examination of Twenty Subjects with Isolated Spinal Cord

Subject	Age	Lesion	Date	Pain Threshold of Hand in Mcal./Sec./Cm.² (3-Sec. Exposures)	"Resting" Reflex Movement Threshold in Mcal./Sec./Cm.² (3-Sec. Exposures)	
					Thigh	Foot
L. McL.	22	T5 (gunshot wound)	12/20/51	230	240	250
			1/30/52	240	260	270
			1/31/52	240	260	290
			2/15/52	210	330	...
			6/ 4/52	220	430	360
J. P.	24	C5 (gunshot wound)	1/21/52	190	240	...
			2/13/52	200	250	...
F. L.	59	T5 (tumor)	1/28/52	220	380	...
			2/ 5/52	210	250	320
			2/21/52	230	270	...
M. McG.	27	T7 (gunshot wound)	2/ 5/52	210	230	...
			3/ 3/52	210	270	...
			3/ 7/52	230	300	...
			3/11/52	215	230	...
L. A.	22	T8 (fracture)	2/15/52	235	310	360
C. S.	58	T7 (tumor)	2/28/52	200	300	415
			4/ 8/52	230	270	340
E. N.	20	T6 (gunshot wound)	2/29/52	200	280	...
C. R.	20	T8 (gunshot wound)	3/12/54	230	330	...
M. S.	27	T2 (fracture)	3/25/52	220	400	280
E. B.	22	T7 (fracture)	4/ 1/52	220	410	...
A. B.	21	T10 (gunshot wound)	4/ 3/52	210	...	380
J. F.	24	T5 (fracture)	4/15/52	200	280	300
			4/18/52	210	260	300
			5/23/52	210 to 220	...	260
S. S.	25	C5 (gunshot wound)	6/ 9/52	...	290	...
M. G.	21	T10 (fracture)	6/26/52	240	410	...
L. R.	21	T5 (gunshot wound)	6/30/52	200	260	...
D. B.	22	T4 (fracture)	7/13/53	220	370	...
			1/20/54	...	400	...
R. L.	25	T1 (fracture)	7/19/53	200	350	...
W. Y.	23	T5 (gunshot wound)	11/ 3/53	210	240	...
J. H.	38	T7 (gunshot wound)	11/18/53	250	320	...
J. P.	31	T10 (gunshot wound)	12/29/53	240	330	...

Methods.—The subjects were treated while lying on their backs on a stretcher in a quiet room at a constant temperature of 21 to 25 C. The Hardy-Wolff-Goodell dolorimeter was used to provide thermal stimuli of measured intensity.[4] Pain thresholds were measured by exposing the blackened skin of a normally innervated segment above the level of the lesion to thermal radiation for three seconds and by recording the amount of radiation in milli-

calories per second per square centimeter which just produced pain sensation. Similarly, the minimal intensity of thermal stimulation measured in millicalories per second per square centimeter necessary to evoke a movement in the paraplegic limb was ascertained, and this value was designated the reflex movement threshold, hereafter referred to as the RMT. Large areas of the interior surfaces of the feet and thighs were blackened and were stimulated by applying thermal radiation for three seconds. No single skin site was stimulated more than once, thus avoiding the possible effects of heating or injuring the skin upon the measurements of the reflex movement phenomena. The pattern of reflex movement responses to such stimulation generally consisted of successive flexor withdrawal, i. e., dorsiflexion of the toes, followed by dorsiflexion of the foot, then flexion of the leg on the thigh, and finally flexion of the thigh at the hip. Occasionally there was simultaneous flexor withdrawal of the opposite limb. Reflex movements were estimated as from 1+ to 4+, 1+ signifying a minimal movement of the toes alone and 4+, a movement of the toes, foot, leg, and thigh. Skin temperatures were measured by means of a Hardy dermal radiometer.

A Harvard inductorium was used for long-sustained noxious stimulation. Sustained noxious stimulation in paraplegic patients was also produced by distension of the urinary bladder with ±500 cc. of water.

The effects of a single intramuscular injection of morphine sulfate upon the reflex movement threshold were observed.

OBSERVATIONS

SERIES I.—*The pain threshold in normally innervated skin above the level of the spinal cord lesion was within the normal range and did not vary from day to day in these 20 paraplegic subjects.*

The pain threshold was measured in various dermatomes above the level of the spinal cord lesion: the forehead, the dorsum of the hand, and the shoulder. No significant variation was obtained from patient to patient or in the same patient from day to day. This series of pain thresholds was in the range of 220±20 mcal. per second per square centimeter (Table).

SERIES II.—*At the beginning of a period of testing, the reflex movement threshold was sometimes close to, but always above, the value of the pain threshold of normally innervated dermatomes.*

The reflex movement threshold (hereafter designated as RMT) was measured in two areas, the thigh and the foot, below the level of the spinal cord lesion, and these values were compared with the values for the pain threshold of intact dermatomes. In 7 of the 20 subjects the RMT of the paraplegic extremities at the beginning of one period of observation was approximately the same as the pain thresholds in intact dermatomes. The RMT's were 10 to 50 mcal. above the pain threshold in these patients.

In the remaining 13 subjects, the RMT's were more markedly elevated above the pain thresholds of intact dermatomes. The differences ranged from 70 to 210 mcal., and the values are given in the accompanying Table. That variation in skin temperature did not account for differences in RMT is demonstrated below.

Comment.—In these resting paraplegic subjects, who for a period of 30 to 60 minutes had not been noxiously stimulated either experimentally or spontaneously, the stimulation which could evoke reflex movement had to be noxious. A similar observation was made by Hardy on one paraplegic subject. The reflex movement was evoked approximately at the critical skin temperature for the pain threshold, 44.5±1

C.† Hardy's hypothesis, that the motor response to a thermal stimulus in a paraplegic subject is directly related to the critical skin temperature for pain threshold, has been explored further in observations on 20 subjects. Evidence has been accumulated which indicates that the reflex movement threshold is variable and that this variability is dependent upon the level of central excitation in the isolated spinal cord.

SERIES III.—*In contrast to the day-to-day uniformity of the pain threshold in normally innervated dermatomes, the initial RMT of resting subjects in the dermatomes below the level of the spinal cord lesion exhibited marked variability.*

Measurements of the RMT were made in the same dermatomes in six subjects on two or more days. The initial RMT's of Subject L. McL. on five different days ranged from 240 to 430 mcal. (Table). Similarly, the initial RMT of Subject F. L. varied from 250 to 380 mcal. on three different days, and the RMT's of Subject C. S. varied from 270 to 415 mcal. on two different days. These RMT's were measured after a 30- to 60-minute period of rest, completely free of noxious stimulation. .

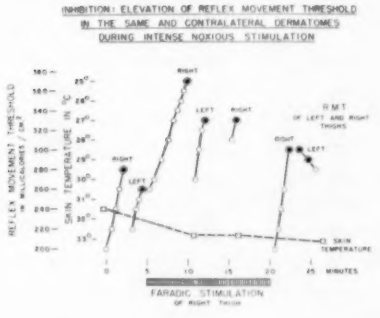

Figure 1

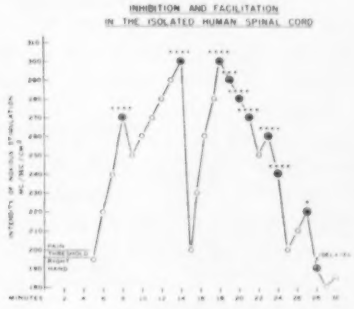

Figure 2

Comment.—It has been demonstrated that pain in the undamaged skin is evoked at a critical level of skin temperature, i. e., 44.5 ± 1 C., and that gross differences in skin temperature are reflected in the amount of thermal energy required to raise the skin temperature to the critical level of the pain threshold. It has been calculated that for a 1 C. change in the skin temperature there will be an approximate difference of 20 mcal. in the amount of thermal energy required to raise skin temperature to the critical level of pain threshold.[6] As mentioned above, it has been anticipated that the RMT in a resting paraplegic subject would closely approximate the pain threshold of normally innervated dermatomes. The difference of pain threshold and RMT and the marked variability of the RMT prompted further exploration of the relationship between skin temperatures and the RMT.

SERIES IV.—*Major fluctuations in the RMT were not significantly related to variations in skin temperature.*

† References 5 and 6.

Skin temperatures were recorded in the test areas of 10 subjects immediately before and just after the measurement of the RMT. In Subject J. F. frequent three-second stimuli were applied in a two-hour period, during which skin temperature of the right thigh ranged from 30 to 32.8 C. and the RMT, from 220 to 380 mcal. per second per square centimeter (Fig. 1). There was no correlation between fluctuation of the RMT and the variations in the skin temperature.

In subject M. McG. the initial RMT of the left thigh was 270 mcal. per second per square centimeter. Within the next 25 minutes, after applying 25 equally spaced thermal stimuli of three seconds' duration but of varying intensities, the RMT was lowered to 140 mcal. per second per square centimeter and the skin temperature had changed from an initial level of 32.5 to 34.0 C. (Fig. 2).

Subject C. R. had a lowering of the RMT of the right thigh from 330 to 210 mcal. after 25 stimuli of three seconds' duration applied on separate skin sites over a large area in a 14-minute period. However, during that same period the skin tem-

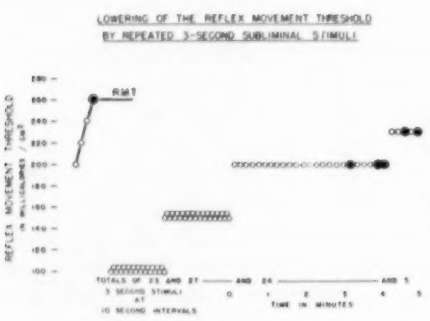

Figure 3

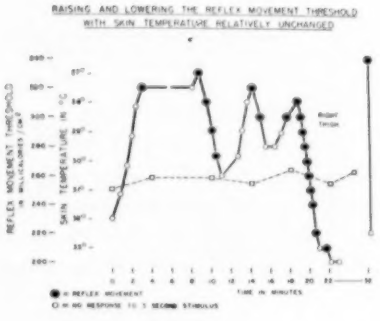

Figure 4

perature of the tested area varied only from 30.4 to 30.7 C. (Fig. 3). In Subject M. S. the initial RMT on the right thigh was 400 mcal. After a series of stimuli applied in a 10-minute period, it was lowered to 280 mcal. (Fig. 4). The RMT of adjacent and contralateral dermatomes was similarly lowered. The skin temperature of the right thigh was elevated in this same 10-minute period from 30.8 to 31.8 C.

Comment.—The degree and direction of change in the skin temperature have not accounted for the gross variations in the amount of thermal radiation necessary to evoke a reflex movement in these paraplegic subjects. For instance, in Subject J. F., cited above with a lowering of the skin temperature of 2.8 C., the RMT, if closely related to skin temperature on the basis of 20 mcal. per 1 C. change in skin temperature, would have been expected to be raised from an initial 380 mcal. to approximately 440 mcal. But, in reality, the RMT was "lowered" as much as 160 mcal., i. e., from 380 to 220 mcal.

This, and the other examples cited, demonstrated that changes in skin temperature did not account for the changes in RMT. In several hundred measurements

of skin temperatures made on 10 subjects, it was repeatedly observed that either a raising or lowering of the RMT could occur without relationship to the direction and amount of change in skin temperature.

SERIES V.—*The RMT could be elevated; i. e., the intensity of a thermal stimulus that was initially adequate to evoke a reflex movement may no longer be adequate after a short interval of time and may have to be increased in order to elicit a second reflex movement.*

At the beginning of a period of observations following a rest period of 30 to 60 minutes, the RMT was measured. Often when a stimulus of the same intensity as that of the initial RMT was reapplied one to five minutes later, no reflex movement was elicited (Fig. 3). Successive stimuli had to be increased from 10 to 50 mcal. to become effective again in evoking reflex movement. This phenomenon of raising the reflex movement threshold was observed in 15 subjects.

SERIES VI.—*In contrast to the observations of Series V, the RMT could be progressively lowered by repeated adequate stimulation.*

When the RMT had been ascertained, subsequent applications of thermal stimulation of the same or greater intensity repeated at short intervals were usually found to lower the RMT (Figs. 2, 3, and 5). Thus, the intensity of the stimulus adequate to elicit reflex movement could be progressively lowered until the RMT was reduced as much as 60 to 160 mcal. per second per square centimeter below the initial RMT. In five subjects with initial RMT's of 310, 270, 270, 250, and 230 mcal., the RMT was lowered even below the level of the pain thresholds of intact dermatomes, i. e., to 150, 150, 140, 160, and 140 mcal. per second per square centimeter, respectively. At this point, in each of these five subjects, it was possible to elicit a flexor movement by briefly and gently blowing upon the skin of the extremity or by touching any part of the extremity with a whisp of cotton. The lowering of the RMT below the level of pain threshold was repeatedly demonstrated in each of these five subjects (Fig. 2).

It was, however, observed that the RMT could not be precipitously lowered; instead, it was necessary to apply a series of effective stimuli with small decrements of intensity in order to lower the RMT significantly. Thus, in Subject E. N. (Fig. 5), when his RMT was at 300 mcal., a subsequent stimulus of 200 mcal. failed to elicit a motor response, but after the application of a series of effective stimuli with decrements in intensity of only 10 to 20 mcal. a stimulus of 190 mcal. became effective. This same phenomenon was apparent in all subjects and is demonstrated also in the observations in Subjects McG. and C. R. (Figs. 2 and 3).

Comment.—In general, in these 20 patients, the initial RMT was considerably elevated above the level of pain threshold of their intact dermatomes. As noted in Series V, the minimal stimulus adequate to elicit reflex movement often was inadequate to elicit movement on a second trial. It was sometimes necessary to increase the intensity of stimulus by several increments of 10 to 20 mcal. before a new and thus further elevated threshold of reflex movement would be found. In order to explain this phenomenon, it has been inferred that the state of excitation in the spinal cord had been so altered by the occurrence of the initial reflex movement that a larger barrage of afferent impulses upon the cord was necessary before another reflex movement could be elicited. However, once this refractory state had

been overcome, it was possible to effect a lowering of the RMT toward pain threshold levels, and in many instances even well below the level of pain threshold, by applying a series of adequate stimuli of gradually decreasing intensities.

It is postulated that such a state of central hyperexcitability had been established that tactile and temperature stimuli, either warm or cool, which were far out of the range of the level of noxious intensity were capable of producing reflex movement. Thus, there is developed a widespread excitation within the isolated spinal cord which prepares the neural apparatus to respond to a variety of incoming impulses which are ordinarily inadequate to effect a motor response. This fact may explain the hyperirritability and spontaneous clonic movements sometimes induced in paraplegics by minor stimulation arising from bed sheets or clothes.

SERIES VII.—*A subliminal thermal stimulus repeatedly applied may become adequate to elicit reflex movement.*

The preceding observations have revealed that, by applying in rapid sequence a series of thermal stimuli that are adequate to evoke involuntary movements of

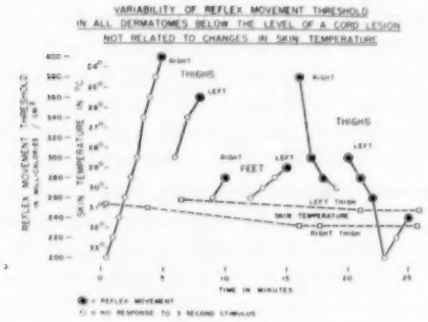

Figure 5

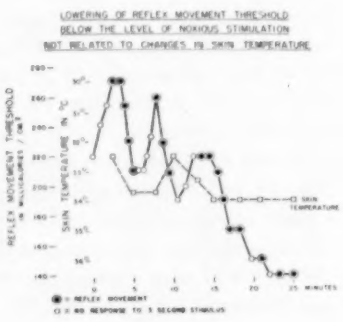
LOWERING OF REFLEX MOVEMENT THRESHOLD
BELOW THE LEVEL OF NOXIOUS STIMULATION
NOT RELATED TO CHANGES IN SKIN TEMPERATURE
REFLEX MOVEMENT THRESHOLD IN MILLIGRAMS / SQ. CM.
SKIN TEMPERATURE IN °C.
SKIN TEMPERATURE
= REFLEX MOVEMENT
O = NO RESPONSE TO 3 SECOND STIMULUS

Figure 6

the paraplegic limb, such a state of central excitation is developed that the intensity of a stimulus adequate to induce reflex movement becomes less. However, it appeared advisable to investigate whether the cutaneous thermal stimuli themselves, independent of kinesthetic stimuli resulting from reflex movements of the limbs, were capable of altering these states of excitation. Therefore, thermal stimuli that were below the level of the RMT, i. e., inadequate at the existing level of central excitation to evoke a reflex movement, were applied to skin areas on paraplegic limbs repeatedly at regular intervals. A very large blackened area of skin measuring approximately 15 by 20 cm. was used, and care was taken not to stimulate any one site more than once. Thus, after ascertaining the RMT of Subject F. L. to be 260 mcal. on the dorsum of the right foot, subsequent stimulation of 100 mcal. intensity repeated 23 times at 10-second intervals and followed by a series of 27 stimuli of 3-second duration repeated at 10-second intervals at an intensity of 150 mcal. failed to evoke a reflex movement. However, when a 200 mcal. stimulus of 3-second duration was applied, also at 10-second intervals to different areas over the dorsum of the right foot, a motor response occurred on the 19th, and again on the 23d,

stimulus. When a stimulus of 230 mcal. per second per square centimeter was applied at 10-second intervals, it was found that a reflex movement of the right leg occurred on the third and fifth trials (Fig. 6). In another patient (L. McL.) the RMT of the right foot was 430 mcal. per second per square centimeter initially. When a 300 mcal. stimulus was applied to the same foot, it failed to elicit reflex movement, but after applying the 300 mcal. stimulus repeatedly at 10-second intervals, the 15th stimulus evoked a 4+ motor response of the extremity.

Comment.—A series of subliminal thermal stimuli applied to the skin repeatedly at short regular intervals is capable of altering the state of reactivity of the isolated spinal cord. Stimuli thus applied are initially inadequate to evoke a motor response but ultimately elicit motor responses. Under these circumstances it is obvious that the major source of repetitive stimuli is the skin and not from other sources, such as the kinesthetic receptors. Furthermore, there were 10-second intervals between stimuli. This is significant in that it reveals that in the isolated spinal cord states of heightened excitation may develop in response to stimuli widely spaced in time and

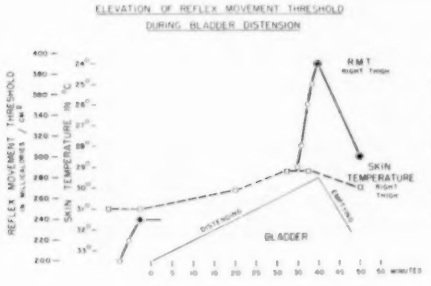

Figure 7

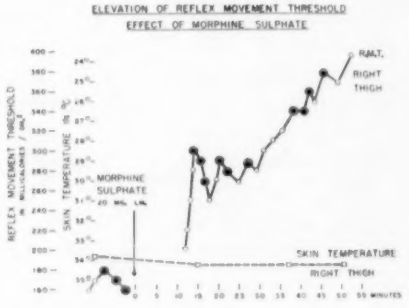

Figure 8

that changes in central excitation can be maintained for seconds or minutes. This is in contrast to the time-values usually recorded in electroneurophysiologic experiments involving one or very few synaptic responses. These relatively long time intervals between stimulation and the protracted alterations of central excitability indicate the sustained modifications of reactivity that can be induced in the neural mass of the isolated cord.

SERIES VIII.—*When repeated thermal stimuli lowered the RMT in one dermatome, the RMT's of other dermatomes in the same and contralateral extremities were also lowered.*

Experiments were designed to ascertain whether excitation set up by stimuli entering one dermatome affected the RMT of only that dermatome or spread to affect the RMT of other dermatomes. It was found, at the beginning of one experiment, in Subject M. S., that the RMT of the right thigh was 400 mcal. and that of the left thigh 360 mcal. Within the next 12 minutes, a total of 10 stimuli varying from 200 to 380 mcal. were applied to the right thigh and both feet, and there occurred five reflex motor reactions. During this period the RMT of the right thigh

was lowered from 400 to 280 mcal. At that point it was found that, despite the 12-minute absence of stimulation of the left thigh, the RMT of the left thigh had been lowered from 360 mcal. at the beginning of the experiment to 300 mcal. (Fig. 4). Similarly, in another patient (C. S.), the RMT of the right thigh was 210 mcal. Eight effective stimuli (300 to 320 mcal.) were applied during the next nine minutes to the right foot. The RMT of the right thigh immediately thereafter was found to have been lowered to 160 mcal. (Fig. 7).

SERIES IX.—*Prolonged continuous high-intensity noxious stimulation of the skin usually raised the RMT in the same and adjacent dermatomes.*

Sherrington observed that when a faradic electric current was continuously applied to the hindlimb of a spinal dog, there was immediate movement of the leg and then the movement ceased, despite the continuing stimulation.[7] In the present investigation of 10 paraplegic subjects, a highly noxious faradic current generated by a Harvard inductorium was applied to paraplegic limbs. This stimulus caused

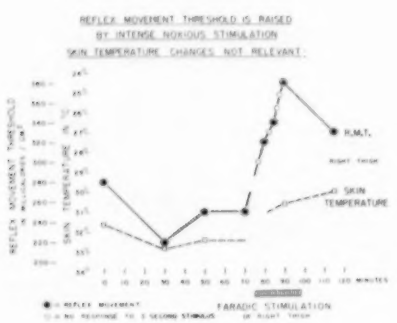

Figure 9

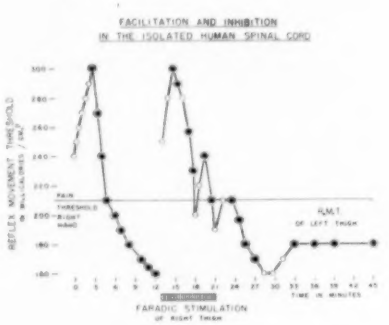

Figure 10

a marked erythema and an extensive pilomotor reaction about the site of application. It was intensely painful when applied to the normally innervated skin. When the stimulus was applied continuously to the paraplegic limb for as long as 15 minutes, there was an involuntary movement only at the beginning of the stimulation, and, thereafter, the faradization evoked no additional movement. Measurement of the RMT's in all dermatomes below the level of the lesion during the period of faradization revealed that in seven out of nine subjects the RMT in all dermatomes tested was raised; in one instance it was lowered, and in one it was unchanged. For example, in Subject M. S., the RMT's of the right and left thighs were 280 and 260 mcal. per second per square centimeter, respectively. As faradization was proceeding on the right thigh, the RMT of the right and the left thigh rose to 370 and 330 mcal., respectively. With this elevation of the RMT's, the skin was warmer rather than cooler (Fig. 8). In another subject (M. McG.), the RMT of the left thigh had been lowered to 160 mcal. by a series of adequate stimuli at short intervals. Immediately after the application of highly noxious faradic stimulation to the right thigh, the RMT of the left thigh was raised to 300 mcal. On the other hand, it was found that, by repeated intense thermal stimulation at short intervals during the

period of faradic stimulation, the RMT could be lowered as it was in Series VI (Fig. 9). The elevation of the RMT by faradic stimulation was also demonstrated in J. F. (Fig. 1).

Comment.—It therefore appears that when there is a high-intensity continuous noxious stimulation of one area below the level of the spinal cord lesion the RMT of other areas is raised (Figs. 1, 8, and 9).

Faradization of the skin constitutes a series of electric shocks delivered at a frequency of approximately 10 per second. A careful study of the effects of faradization of afferent nerves has been made by Jefferson and Schlapp,[8] using cats with transected spinal cords. These investigators were able to demonstrate a critical frequency at which a depression of intraspinal reflex conduction began to occur. As the frequency of stimulation of the posterior tibial nerve progressively exceeded 20 shocks per minute, there was a correspondingly progressive depression of monosynaptic and polysynaptic reflex activity, as recorded from the ventral roots.

These observations may be relevant to the present data concerning the effects of faradization upon reflex movement threshold in human paraplegics. The initial elevation of the RMT of the segment stimulated, as well as of adjoining and contralateral segments, probably represents widespread depression (or "inhibition") of reflex activity by a high-frequency barrage of afferent impulses. Furthermore, three-second thermal stimuli, adequate to evoke reflex movement applied in other dermatomes at short intervals during the faradization, lowered the reflex movement threshold. Thus, it was demonstrated that this depression of reflex activity could be overcome in one area at the same time that a massive barrage of afferent impulses were entering the cord from another dermatome.

SERIES X.—*Prolonged continuous noxious stimulation by distension of the bladder of paraplegic subjects was followed by an elevation of the RMT in all dermatomes below the spinal cord lesion.*

In five paraplegic subjects with lesions at T4, T5 (two), and C6 (two), the RMT was measured in various dermatomes below the level of the spinal cord lesion. Then, in the next 30 minutes, 250 to 800 cc. of sterile water was run into the bladder through a #16 Foley indwelling catheter. The water was contained in a glass reservoir, held high enough to raise the intravesical pressure to 40 to 90 mm. of mercury. During the period of increased intravesical pressure, the RMT of all dermatomes below the level of the lesion became markedly elevated. For example, in Subject S. S., with a lesion at C5, the initial RMT of the right foot was 160 mcal. The bladder was filled with 250 cc. of water during the next 18 minutes, and the intravesical pressure was elevated to 70 mm. of mercury. As bladder distension was continued, the subject reported a throbbing, generalized headache which increased in intensity over the next 18 minutes. At this time, the RMT of the right foot was found to be over 400 mcal. (Fig. 10). The emptying of the bladder was then begun, with immediate relief of the headache. Eight minutes later, the RMT of the right foot was 300 mcal., and 25 minutes later it was 200 mcal.

In order to study the role of skin temperature changes during bladder distension, this experiment was repeated, using Subject W. Y., while recording skin temperatures. This subject, with a spinal cord lesion at T5, showed an RMT on the right thigh of 240 mcal. per second per square centimeter before distension of the bladder.

Skin temperature at this time was 31 C. on the right thigh. Within the next 30 minutes, 500 cc. of water was gradually run into the bladder, raising the intravesical pressure to 40 mm. of mercury. The RMT (Fig. 11) was raised to 390 mcal. per second per square centimeter on the right thigh, with skin temperature in that area at 29.4 C. The bladder was then emptied during a period of eight minutes. On the right thigh, skin temperature was 30 C. and the RMT was 300 mcal.

General Comment on Series VIII, IX, and X.—Experimentally induced changes in the RMT in one dermatome, whether an elevation or a lowering, were associated with similar changes in other dermatomes below the level of the spinal cord lesion. These observations indicate that alterations in the central excitatory state, induced by afferent impulses arising from one source of stimulation, become widespread in the isolated human spinal cord. Sustained and intensely noxious stimulation produced by faradization of the skin or by bladder distension cause widespread elevation of the RMT. It was further observed that during such a period of widespread elevation of the RMT from faradization of the skin, a few intense and adequate thermal stimuli applied in an adjacent dermatome could still produce a temporary lowering of the RMT in that particular dermatome.

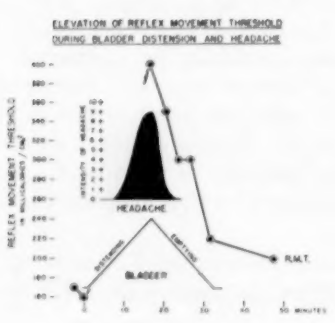

Figure 11

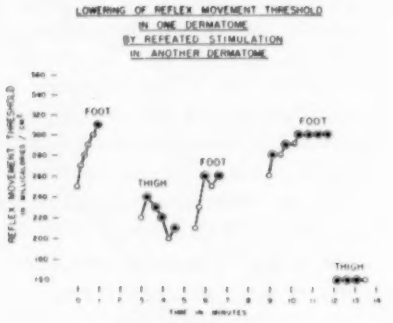

Figure 12

SERIES XI.—*Morphine sulfate raised the RMT of paraplegic subjects.*

The effect of the administration of morphine sulfate upon the RMT was studied in three subjects. All three subjects had loss of sensation and voluntary movement below levels of T4, T7, and T5, respectively. Following a control period of 30 minutes, during which RMT's and skin temperatures were measured, each subject was given 15 mg. of morphine sulfate intramuscularly.

In Subject J. F. the control RMT's from the right and left thighs were 260 mcal. per second per square centimeter. Skin temperatures were 31.2 to 31.9 C. in the areas tested. Morphine sulfate, 15 mg., was administered intramuscularly. Forty minutes later, the RMT's of the thighs were again ascertained and found to be elevated to 320 mcal. per second per square centimeter. Skin temperatures remained unchanged during the period. RMT's remained elevated for an additional 40-minute

period. It was noted that, shortly after administration of the morphine, the frequency and intensity of spontaneous reflex movements decreased, and the subject's legs remained quiet during the 80-minute period of observation.

At the start of the experimental period, the second subject, D. B., was in a state of hyperexcitability, exhibiting spontaneous flexor movements every one to two minutes. The initial RMT of the thigh was 180 mcal. In this state of hyperactivity, stimulation with cotton wool drawn over the skin was adequate to induce reflex movement. Morphine sulfate, 20 mg., was then administered intramuscularly. Within 15 minutes, the RMT on the right thigh was elevated to 300 mcal., and a series of subsequent stimuli did not lower the RMT below 270 mcal. Forty minutes later, the RMT of the right thigh was elevated to such an extent that a 400 mcal. stimulus for three seconds evoked no reflex motor response (Fig. 12). It was also observed in J. F., and in a third subject, J. H., in whom comparable elevation of the RMT occurred following morphine administration, that spontaneous flexor movements were greatly diminished within a few minutes of the injection, and that the legs remained quiet throughout these periods of observation. In none of the three subjects was sleep induced, but in all three there was an elevation of the pain threshold as measured on the dorsum of the hand.

Comment.—These observations in human paraplegic subjects indicate that the depressive action of morphine sulfate on neural activity can occur at the spinal cord level. The data from these experiments are similar to those obtained by Wikler ‡ in dogs with transected spinal cords. With such animals, he observed that the deep tendon reflexes and skin-twitch responses were depressed after administration of morphine sulfate. He concluded that morphine sulfate depresses the activity not only of the highest neural centers, but also of those of the spinal cord.

SUMMARY AND GENERAL COMMENT

Noxious stimulation has been postulated to be the prerequisite for eliciting withdrawal of the lower extremity in animals with transected spinal cords by Creed, Denny-Brown, Eccles, Liddell, and Sherrington.[11] The observations have been made that "injurious heat,"[1] electrical stimulation, pinching and pricking (Sherrington),[1] and direct electrical stimulation of peripheral nerves in dermatomes below the level of a spinal cord lesion[12] evoked flexor withdrawal. Sherrington[1] found that a warm metal plate applied to the limb of a spinal dog evoked no scratch reflex if the temperature of the plate was 65 C. or less; but, to quote, "let it have, when applied, a temperature of 85° [C.] or more, and a reflex is at once vigorously evoked." However, the experimentors have not clarified the interrelationship of timing and intensity of stimulation. In 1952, Macht and Kuhn[2] observed flexor withdrawal of the lower extremities of paraplegic patients when the feet were immersed in water at temperatures of 47.5 C. to 54.0 C. Hence, it has sometimes been inferred that, since a noxious stimulus sets off the first reflex motor response, subsequent stimuli would also have to be noxious to evoke motor response.

It has been demonstrated that for intact persons a painful stimulus is one which is "noxious" or damages tissue at a sufficiently rapid rate. Threshold pain has been

‡ References 9 and 10.

observed to occur when the skin temperature is elevated to 44.5 C. ± 1.0 C. This is also the temperature at which minimal tissue damage, i. e., alteration of tissue proteins, occurs. This relationship was established by measuring, in millicalories per second per square centimeter, the thermal stimulus applied to skin of known temperature which was painful. Variations in skin temperature are thus related to variations in the amount of thermal radiation required to elicit pain, i. e., to raise the skin temperature to the critical temperature of 44.5 C. ± 1.0 C., at which temperature tissue damage occurs and threshold pain is perceived

In all of the subjects of these experiments, the measurements of pain threshold in normally innervated areas were constant within ± 20 mcal., correcting for skin temperature but (also correcting for skin temperature of the area) in dermatomes below the level of cord transection to which thermal stimuli were applied a variation in reflex movement threshold of as much as 250 mcal. was observed.

Thus the cutaneous pain threshold from normally innervated areas occurs at a critical skin temperature within the narrow limits of 44.5 C. ± 1.0 C.; the reflex movement threshold, however, occurs at no such narrowly defined critical level of skin temperature. Instead, in the spinal cord isolated from the regulating influence of higher integrative functions, the RMT varies within wide limits of stimulus intensity, above and below the intensity at which tissue damage is incurred. Furthermore, such wide fluctuation in the threshold of reflex movement was observed in several subjects within periods of 60 minutes. In other words, factors in addition to the intensity of a stimulus determined the occurrence and the intensity of a reflex motor response to stimulation of the skin below the level of the lesion in spinal man. Depending upon the conditions induced by previous stimulation, the RMT was at times elevated or lowered.

Thus, under conditions of "relaxation and rest" and in the absence of cutaneous stimulation that could evoke a motor response, the amount of thermal energy initially required to elicit a reflex movement was sometimes near, but invariably more than, that which would elicit threshold pain in normally innervated areas. However, once a reflex movement had been elicited at a given threshold, it was not possible to predict whether the next reflex movement would be elicited by the same, a higher, or a lower intensity of thermal stimulation. Frequently, when the initial reflex movement threshold was but little elevated above an average pain threshold for normally innervated areas then a second reflex movement could not be evoked by the same stimulus intensity, but one of greater intensity was needed, suggesting that the neurones of the isolated spinal cord had become refractory. On the other hand, when heightened intensity of thermal stimulation, at which a motor response occurred, was applied repeatedly, the intensity of effective thermal stimulation could then be progressively lowered. Indeed, by this procedure of gradually lowering the stimulus intensity, a new and transiently stable threshold of reflex movement considerably below the initial threshold could be demonstrated. This altered state of reactivity was not limited to the dermatome being stimulated, but was widespread, so that when there were changes in the RMT of one dermatome variations of similar direction and magnitude in the RMT's of adjacent and contralateral dermatomes occurred. The lowering of the RMT even below an average pain threshold could

also be demonstrated by repeatedly applying a subliminal, i. e., initially ineffective, stimulus every 10 seconds until a motor response occurred. That the lowering of the RMT occurred as a result of the thermal stimulation of the skin and independently of proprioceptive impulses initiated by motor responses was also demonstrated. With repetition of a thermal stimulus of the same intensity applied at 10-second intervals over a large area of blackened skin (so that no one spot was stimulated more than once), motor responses occurred more and more frequently, until finally almost every stimulus evoked reflex motor response. At this time the stimulus intensity was decreased to a new subliminal level, and again repeated 3-second stimuli applied at 10-second intervals became adequate to evoke a motor response.

At this level of the RMT a noxious stimulus was no longer required to evoke a reflex motor response. Instead, with the existence of such heightened reactivity, non-noxious stimuli, such as blowing on the skin or touching the skin with a wisp of cotton, could elicit a response. Therefore, although noxious cutaneous stimuli giving rise to impulses carried by fibers that mediate pain activate reflex motor responses in spinal man, repeated stimulation in dermatomes below the level of the spinal cord lesion so intensifies and spreads central excitation that impulses carried by fibers subserving nonpainful sensation may at times effect a motor response.

The effects of maintained noxious stimulation of the skin were reported by Sherrington in his study of the scratch reflex.[7] He found that continuous electrical stimulation evoked a flexion reflex in the spinal dog at the moment the stimulus was applied but that thereafter there was no additional movement despite continuing faradic stimulation. In the present study, this finding has been confirmed, but in addition a difference between interrupted and sustained noxious stimulation in their effects on the RMT has been revealed. Thus, thermal stimulation of 3 seconds' duration applied at 10- to 30-second intervals could either raise or lower the RMT, but when noxious stimulation was intense and sustained for minutes by means of faradic stimulation of the skin or by bladder distension an initial motor response was followed by a widespread elevation of the reflex movement threshold. This profound inhibition of reflex movement thresholds in all dermatomes below the level of the spinal cord lesion could in any single dermatome, nevertheless, be overcome by a series of adequate stimuli applied in that same dermatome.

Both the elevation and the lowering of the reflex movement threshold, as has been observed in these experiments, could be produced with stimuli applied at intervals of several seconds or even of several minutes. Furthermore, these alterations in the reflex movement threshold were sustained for seconds, or even for many minutes, after the last stimulus. This is in contrast to the time intervals recorded in most neurophysiological experiments involving few synapses, in which time intervals are measured in milliseconds.

These long-sustained inhibitory or facilitatory effects of stimulation reveal that, even in the relatively small mass of neural tissue of the isolated cord, the modifications of reactivity induced by previous stimulation persist long after the immediate overt reaction to the stimulus.

From the data of these experiments it is postulated that the variability of the RMT is attributable to variations in degree of central excitation within the isolated

spinal cord. The extreme variability of the RMT cannot be explained on the basis of functional changes in the sensory end-organs or in the peripheral nerve, since neither end-organ nor nerve shows such wide variations in thresholds of stimulation. Furthermore, the observations that thermal stimulation of one dermatome raised and lowered the RMT of opposite and adjacent dermatomes and that these changes are maintained for seconds and minutes after stimulation point to changes in intraspinal rather than peripheral neural function. Only masses of neural tissue with extensive multisynaptic connections demonstrate such wide variation in thresholds and such protracted disturbances.

Even if noxious stimulation fails to evoke a motor response, that stimulation nevertheless gives rise to a volley of afferent impulses which alter the responsiveness of the neural equipment of the cord. For example, subliminal cutaneous stimuli that are initially inadequate to cause a motor response can, when rapidly reapplied in series, produce a reflex motor response and, if continued, can elicit progressively more frequent responses. Thus, the isolated spinal cord appears capable of retaining the effects of volleys of afferent impulses in such a way that a state of excitation is gradually built up until it becomes adequate to elicit reflex movement.

Sherrington, in his comments on spinal dogs, mentioned that "conduction along reflex arcs presents features that may be figuratively described as inertia and momentum."[7] Such a state of "inertia" is suggested by the observations that reflex movements are usually not elicited readily in the relaxed subject who has not recently been stimulated.

It has been demonstrated in this study that the "inertia" and "momentum" of reaction to stimulation in the isolated spinal cord represent a state of reactivity that exceeds the bounds of useful adaptation to noxious stimuli. On the one hand, irreversible tissue damage may occur before a defensive motor response is evoked; on the other hand, there may occur excessive and inappropriate reactions to such inconsequential stimuli as light touch or warmth. Therefore, although sustained alterations in the reactivity of the spinal cord occur consequent to peripheral stimulation, nevertheless the isolated spinal cord lacks the capacity to discriminate between noxious and non-noxious stimulation and to regulate the responses so that they are appropriate to the stimulus.

These observations have demonstrated in the isolated spinal cord that the response of the motor system to a peripheral stimulus cannot be equated to the intensity of the stimulus but that motor response is dependent upon a markedly labile state of central excitation modifiable by the timing and intensity of previous stimulation of the periphery. This variability of the level of central excitation has been aptly formulated by Henry Head: "No stimulus however mechanically invaried can evoke a constant response because the very existence of the impulse it produces changes the disposition of the reacting center."[13] However, in the absence of the regulating influence exerted by supraspinal mechanisms, although profound and sustained changes occur in the "disposition of the reacting center," i. e., the isolated spinal cord, they are poorly adapted to the needs of the organism. The isolated cord divorced from the regulatory control of the cerebral hemispheres permits irreversible tissue damage to occur before a defensive response is elicited and yet allows innocuous stimuli to evoke excessive responses.

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Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY AND THE NEW YORK NEUROLOGICAL SOCIETY

Charles Rupp, M.D., and Richard M. Brickner, M.D., *Presiding*
Joint Meeting, April 9, 1954

Cerebral Angiomatous Malformations. Dr. Richard M. Paddison, Dr. Leo Madow, and Dr. William H. Whiteley.

The authors report their experiences in the diagnosis and treatment of angiomatous lesions, six of which were pathologically studied. Ten of the cases were arteriovenous abnormalities, but 2 of the cases were cortical telangiectases.

There were nine male and three female patients in the series. A total of 12 angiomatous lesions were found in a series of 374 brain tumors, an incidence of 3.2%.

Of the 12 cases, 7 presented with convulsive seizures of focal or generalized type; 9 showed various focal neurological signs of hemiparesis, hemiplegia, or aphasia; 5 presented with subarachnoid hemorrhage, and 5 demonstrated headache as an outstanding symptom. In only one case was the presence of bruit demonstrated.

Routine skull x-rays showed calcification in two cases and pineal shift in three cases. Pneumoencephalography performed in three cases was negative. Ventriculography in one case showed the entire ventricular system shifted to the right. Angiography was performed in all cases, and in two of the cases there were no demonstrable angiographic abnormalities.

Carotid ligation was performed in two cases. Craniotomy was performed in 10 cases, with total resection of the lesion in 6 cases. In one case the lesion was unresectable, and in one case the angiomatous malformation could not be demonstrated at operation. In two cases clipping and coagulation of the abnormal vessel was performed. There were no operative deaths.

Eight of the cases were followed for periods up to five and one-half years. One case died of a massive subarachnoid hemorrhage 10 months after carotid ligation. All resected cases had postoperative focal or generalized seizures, but all of them were maintained on anticonvulsant medication.

The fact was stressed that angiography is essential in the diagnosis and localization of cerebral angiomatous malformations. It was felt that radical extirpation of these cerebral lesions is the treatment of choice and that by this method the patient is spared from further bouts of subarachnoid hemorrhage and from further progression of his clinical symptomatology.

DISCUSSION

Dr. Bronson S. Ray: This topic is one of the newer ones in the field of neurology. It certainly has been developed within the last 10 years. I recognize that particularly when I am quoted as recommending carotid ligation, because the paper I wrote was about 12 years ago, and I certainly would not recommend that procedure at the present time.

I had the opportunity of reviewing this paper beforehand; it is a very interesting group of cases. I was particularly interested in the case of telangiectasia in a patient with a Sturge-Weber syndrome.

In our series of cases we did not find anything significantly different in our evaluation of symptoms and other characteristics of the lesion than as reported here, with this possible exception: we did not find such marked discrepancy between males and females. In our series of 33 cases we find that the males only slightly outnumber the females. Also, we have found a bruit in a much higher percentage. I admit that in some cases we have looked for the bruit after we have learned that the lesion was present; but by listening carefully over the eyeball particularly, one can often hear a bruit, whereas it may not be audible over the skull.

We have been disappointed in the use of the radioactive tracer as a means of identifying the presence or location of these lesions. In a half dozen cases, we have found no abnormalities.

Of course, the angiogram has made all these advances possible. The angiogram tells us the location, the general extent, and limitations of the lesion, the principal arteries, and the veins. With that kind of information, we can plot our course.

I would add, however, that I believe that seriograms often aid materially in the study, particularly when the lesions may not show adequately on a single exposure. We have made a practice of employing the seriogram in every patient who shows the lesion on the scout film at the first injection. We had one patient who did not demonstrate a lesion at all on a single film but did on a seriogram.

When it comes to discussing treatment of these patients, we must stop and consider what we expect to accomplish by operation. There are, in general, three groups of symptoms which you have heard that are attributable to these lesions: one is intracranial hemorrhage; another is convulsive seizure, and another is palsy, progressive or episodic and repeated.

The hemorrhages can be severe and serious. They are not commonly fatal, and there are some who will tell you that they know of no fatalities. In our experience we know of two fatalities. One was a young woman who died before we could identify and treat the lesion, and another one was a patient in whom we were able only to resect a part of the lesion. She died about a year later of a massive and recurrent fatal hemorrhage. So hemorrhage is one definite indication for operation, providing the operation does not carry with it the risk of doing damage. If one can get the lesion out without producing unwanted palsy, all right; but if operation means possibly paralyzing the patient, then one would weigh the matter particularly as it suited the individual patient.

With regard to convulsions, one would be cautious about assuming that in excising the lesion he could predict termination of the attacks. In my experience patients are still likely to have fits; maybe not quite as bad, but there is still a problem.

DR. IRWIN FEIGIN: Dr. Paddison and his colleagues have obviously studied their cases with commendable care and the results they have obtained are quite encouraging.

When a pathologist encounters a mass of abnormal blood vessels, he must attempt to decide a number of problems which are not very easy to resolve. He has to determine first, the nature of the vessels with which he is dealing, whether these vessels are present in the form of a congenital malformation, whether they represent a true neoplasm, and also the degree to which their characteristics have been altered by acquired factors.

As far as neoplasms are concerned, these are, fortunately, very rare. I refer to unquestioned neoplasms. When a tumor related to blood vessel is obviously highly anaplastic and metastasizes, as they sometimes, but rarely, do in the general organs, then we know we are dealing with a neoplasm. Under other circumstances this decision is very difficult to make. Even a tumor as well-defined as the hemangioblastoma of the cerebellum is one to which many men have ascribed different characteristics. Some consider this to be a true neoplasm; many others deny this and claim it represents a malformation.

Even the presence of large numbers of cells in addition to blood vessels does not necessarily indicate that we are dealing with a neoplasm. Juvenile angiomas of the skin, for example, which are often highly cellular, are not neoplasms, and they disappear at about puberty.

I think that the tumors that have been dealt with this afternoon are all malformations. The term "malformation" should not imply that this mass of vessels was present in this form since birth. The fact that a definite arteriovenous communication is first observed at the age of 30 makes this most unlikely. The possibility exists that many of these started as venous angiomas, over the course of years enlarged somewhat, and in some way came into contact with small arteries which were incorporated into the mass. The arterial blood was then permitted to enter these venous channels. Following this, of course, the pressure of arterial blood then accelerated the process and serious symptoms appeared at this late date.

It is very much simpler, by the way, for the surgeon to recognize that he is dealing with an arteriovenous angioma or malformation than it is for the pathologist. It is not always easy to differentiate a vein from an artery—simple as that may be when they are both normal—when they have undergone changes. A vein within whose lumen the pressure has been increased by

virtue of a communication with an artery will react to this increased pressure. Its wall will become thickened and fibrotic, its muscle hypertrophied, and elastic tissue will be increased, though it may not assume the form of a discrete elastic membrane.

Similarly, an artery which is the site of a pathological process may have its wall altered to a degree which would make it very closely resemble an altered vein of the type described.

When we exclude the possibility of a true neoplasm, these patients are benefited to the degree to which the surgeons can remove the lesion, or at least prevent a further extension of the damage which results by arterialization of these angiomas.

DR. RICHARD M. PADDISON: Our incidence as far as sexual distribution was nine males to three females, which seems to go along with most of the series in the literature. Regarding the bruit that my colleague, Dr. Whiteley, is a "bug" on—and he listens assiduously, both before and after angiograms—we only found that one.

In regard to Dr. Feigin's comments, it is difficult to determine pathologically just exactly what is going on in these vessels and also what is the communication that existed in vivo.

One other comment, we have noted in the cases in which we have cortical material to examine that there are changes in the underlying cortex, too. In the 4-year-old boy there were changes in his cortical arterioles such that, if you were given this artery out of context, you would call it cerebral arteriosclerosis.

Experiences with Direct Surgical Treatment of Intracranial Aneurysms. DR. ROBERT A. GROFF.

Thirty-eight intracranial aneurysms were subjected to direct surgical therapy. There were 22 on internal carotid artery, 6 anterior cerebral, 3 posterior communicating and anterior communicating, 2 on middle cerebral and vertebral, and 1 auditory artery.

Thirty aneurysms were "trapped," that is, occluding the vessel on either side of the origin or the stalk. In four the sac was packed with muscle, and in four no specific therapy was done.

There were eight deaths, a mortality of 22.2%. The location of these aneurysms was anterior communicating 3; anterior cerebral 2; superior cerebellar 1; vertebral 1, and multiple 1, the untreated rupturing five months after surgery.

The postoperative complications consisted of hemiplegia 4, convulsions 6, and mental changes in those in which the internal carotid artery or anterior cerebral artery was occluded. All cleared except one hemiplegia, which improved to a hemiparesis. The mental changes disappeared in two to four months.

Direct surgical therapy is the only certain method of curing the lesion and is reasonably safe. Where an aneurysm is suspected, therefore, arteriography should be performed five to seven days after the initial bleeding, or earlier if the condition of the patient demands. Bilateral arteriography should be done to establish multiple lesions as well as the status of cerebral circulation. If the aneurysm is on the internal carotid artery, the common carotid should be ligated in the neck with usual precautions, and seven days later the internal carotid or the aneurysm should be attacked directly. It is felt that ligation of the common and/or internal carotid artery serves no useful purpose in the treatment of aneurysms in other locations.

DISCUSSION

DR. LESTER A. MOUNT: Many neurosurgeons and many neurologists agree with Dr. Groff that the best method of treatment of intracranial aneurysms is surgical therapy, that is, to ligate the carotid arteries or to isolate and completely remove them from circulation. For, as Gowers said in 1892, if the diagnosis of an intracranial aneurysm is certain, the prognosis is extremely grave, for no one knows how near or how far may be a fatal rupture.

Dr. Groff has demonstrated how important it is to have bilateral arteriography before operative therapy is given. This is necessary not only to demonstrate the site of the aneurysm or aneurysms but also to show the collateral circulation and the degree of arterial spasm. To know the degree of arterial spasm is necessary in all cases with a recent hemorrhage, and its presence may result in failure of operative therapy.

This brings us to the time when operative therapy should be undertaken. Olivecrona says three weeks from the time of the hemorrhage. Dr. Groff has mentioned in his paper that, when it is possible, to wait 5 to 7 days after bleeding to do the arteriogram.

We have tried to judge every case on its own merit, but a good way to express it would be to proceed as soon as there is a reasonable possibility of having a good result. This means from 2 to 3 days to 2 to 3 weeks after the hemorrhage has occurred, that is, the initial hemorrhage.

Our results have not been sufficiently rewarding to encourage us to proceed with arteriography and operative therapy in patients that are continually bleeding and are in poor physical condition. We have had patients who have appeared in danger of death but who have improved, and definitive surgical therapy has been then administered with satisfying results.

As Dr. Groff has already explained, the cases in which he has done carotid ligation have been those cases which he did not consider satisfactory for an intracranial approach, or where general physical condition at the time was not sufficiently good. Of course, this can account for the higher mortality rate than that of those patients who had the carotid ligation alone. We have had some cases that have had very satisfactory results from carotid ligation alone, even on the middle cerebral artery. The exact place or effectiveness of carotid ligation alone has really not yet been entirely established, but if we would all do arteriography about three months after the ligation has been performed, perhaps we would get a little bit nearer to the answer.

Also, if we would pool all our results of the various methods of therapy, or publish them as Dr. Roth has done, we would then be able to determine the indications and the counterindications of the various methods of therapy.

Dr. Sidney W. Gross: We have used carotid ligation as the method of choice in the treatment of most of our patients. The direct surgical attack has been used in special circumstances. If the aneurysm is associated with a sizeable intracerebral hemorrhage—in other words, if the angiogram in addition to an aneurysm shows a marked dislocation of the middle cerebral or anterior cerebral artery, indicating a sizeable intracerebral hematoma—then we have resorted to the direct surgical approach.

The direct surgical attack is also used in patients who do not tolerate carotid compression and who develop signs of inadequate circulation manifested by seizures, coma, or hemiplegia. This applies also to cases in which the aneurysm fills from both sides and in which, of course, the ligation of one carotid artery could have very little, if any, effect.

We have now followed patients who have had carotid ligation for 10 years and more; some were ligated as early as 1939. In my own series, I know of no patient who had a carotid ligation for an aneurysm and in whom bleeding occurred following ligation.

We feel that if an aneurysm is demonstrated in the anterior portion of the circle of Willis and the patient tolerates ligation of the common carotid artery, there are chances of good results from carotid ligation alone, with a relatively low incidence of complication and a very low mortality rate among those in reasonably good condition. I am not talking about the patient who comes in moribund and who manifestly will have a high mortality under any regimen, whether the aneurysm is attacked directly or ligated.

The problem comes up as to when to do arteriography. When patients on admission are in the acute phase with stiff neck, fever, and coma, an arteriogram may be quite hazardous. In such cases, we consider it advisable to watch the patient, at least for a few days. If there is no improvement, then an arteriogram should be made because of moral compunctions and the lack of an alternative. If improvement is evident, it is best to do the arteriogram between the 7th and the 10th day; it certainly should be done before two weeks has elapsed. Our experience thus far has been, and I believe others have also noted, that patients who bleed again while in the hospital will usually have another hemorrhage between the second and the third week. This definitely has been our experience when, for one reason or another, there was a delay.

In the treatment of these lesions, the role of carotid ligation is still open to a good deal of discussion. Only further experience and collected experience, as Dr. Mount suggests, over the next few years will furnish us with the information needed to finally determine which will be the method of choice.

Observations on Ventricular and Lumbar Subarachnoid Peritoneal Shunts in Hydrocephalus in Infants. DR. MICHAEL SCOTT, DR. HENRY T. WYCIS, DR. FREDERICK MURTAGH, and DR. VICTOR REYES (by invitation).

Most shunts failed because of blockage in the peritoneal cavity. The so-called "nonirritating plastics" created renewed efforts. Since 1950 we have operated on 29 hydrocephalic infants, 8 noncommunicating, 21 communicating. The etiology included 15 congenital, 5 with myelodysplasia. Ninety-three per cent were 1 to 12 months of age.

The cerebral mantle measured from air studies was between 0.5 to 2.0 cm. in 72%. The following shunts were done: ventricular peritoneal 9 (11 revisions); subdural peritoneal 1 (2 revisions); lumbar peritoneal 16 (12 revisions), and miscellaneous 3 (6 revisions).

The following materials were used: (1) Cortex (vinyl plastic); (2) polyethylene; (3) stainless steel button; (4) Davol #9 rubber tubing, and (5) stainless steel hollow screw in lumbar vertebra.

Twenty-nine infants had original shunt operations. There were 26 revisions; a total of 59 operations. There were nine deaths (case mortality of 31%). There were three postoperative deaths (operative mortality of 5.4%). Of 29 infants, 20 survived operation. Out of 21 with communicating hydrocephalus, 18 survived surgery.

Seven patients were followed less than one year and hydrocephalus controlled in all. Eight were followed one to three years, and the hydrocephalus controlled in seven. However, four are of good mentality and three of poor mentality. Five patients were followed three to four years. The hydrocephalus controlled in all but one. The mentality was good in two and poor in three.

The causes for blockage are (1) omentum; (2) breaking of tube (especially portex); (3) kinking of tube (polyethylene); (4) fibrous capsule; (5) plug of brain or other tissue, and (6) migration of tube.

The results are unpredictable and blockage of the system in the peritoneal cavity is frequent. Omentectomy may prevent blockage in some cases. However, the interplay of ventricular and intraperitoneal pressure may be an additional factor for blockage and we are investigating this aspect.

DISCUSSION

DR. JOSEPH RANSOHOFF: I became interested in this problem about 1950. Since I worked in the same institution with Dr. Scarff, and thereby inherited some of the unsuccessful choroid plexectomies to do shunt operations on, one thing struck me which explains the number of revisions that have been necessary in Dr. Scott's group. If one does a plexectomy bilaterally and is unsuccessful, one can rather gracefully withdraw from the situation, explaining to the family that little else can be done and that the child cannot survive. This is in contrast with what happens after a shunting operation. In a child who has had relief of intracranial hypertension, which goes along with the hydrocephalus, by a shunting operation, no matter which one, when this tube becomes blocked you then have a real surgical emergency on your hands. The family suddenly appears at the clinic with the child vomiting and acting as if he were obstructed, which in fact he is. In this situation it is very difficult to withdraw gracefully.

Our first operations for shunting were those of ventricular-peritoneal or lumbar-peritoneal anastomoses. Our conception of this problem is that the omentum is probably the factor which produces most of the difficulty. Therefore, we look for a place in the abdominal cavity where we could put these tubes which would be away from the omentum and thereby struck upon the idea of placing them in the suprahepatic area, that is, over the liver, under the diaphragm, where the fluid has free egress to the peritoneal cavity, and yet cannot be reached by the omentum.

Six out of eight of these have gone over a year with satisfactory results. Two were failures. One needed a revision because of growth. This was a ventricular suprahepatic shunt, and the child outgrew the tube which had to be replaced.

Of course, this part of the problem can be solved in the communicating hydrocephalus by simply using the lumbar space, or in an obstructive hydrocephalus by first doing a Torkildsen and then doing the lumbar subarachnoid shunt. The growth factor is a difficult one to handle if one plans to place a tube from the ventricle down.

We were beginning to think about the possibility of putting tubes into the pleural cavity. The growth factor from the ventricle to the apex or the upper area of the pleura between an adult and a hydrocephalic child is very small.

About this time as we were attempting to get into the suprahepatic space, which is approached through the bed of the 12th rib, we accidentally got into the pleura and thus arrived our first ventricular-pleural shunt. That was in 1951 and that child is still doing well. We have done 28 ventricular-pleural operations, and in this group there have been 8 complete failures. There have been four additional children who needed one revision. This does not give you the total number of revisions. I do not have the figure but it is very large, because in some of the children who were complete failures we carried out a number of procedures.

There is, however, a group, as you can see, which has been successfully able to handle the hydrocephalus by shunting the fluid into the pleural cavity.

As far as the materials used, we have used Portex fairly exclusively, and the longest Portex case is since 1951. So far the tube has not cracked, although I am going to worry about it from now on. Rubber actually is the most satisfactory tube to be used. Our problem in the failures of pleura cases has been the inability of the child to absorb.

There is only one additional point I would like to make with reference to the shunting operations, and that is that a number of the children had to have repeated procedures. One child in particular who has had eight different shunting operations during a three-year interval, coming in repeatedly with acute attacks of obstructive hydrocephalus, is still a good child. The child is now five years old, is going to kindergarten, has an I. Q. of over 100—this in spite of the fact he has spent more of his time in the Neurological Institute than he has at home since his development of hydrocephalus, which was at the age of a little over a year.

If one is willing to fight it out with these children, one can salvage a fairly high number. Some workers believe that if children can be relieved of hydrocephalus for a period of two or three years, they will spontaneously take over themselves. This may justify the number of revisions. I have yet, however, not seen this happy result. Any time I have seen a tube blocked or have been able to demonstrate that a tube was blocked, the child was sick. I have not yet seen any children who have had a shunting operation who subsequently recovered from their hydrocephalus with the tube being blocked.

This is a very serious criticism of the procedure as contrasted, for example, with choroid plexectomy, where the possibility of the child developing its own pathway for absorption of the fluid exists. Once you put a tube in, you commit that child to utilizing the shunting procedure, and the possibility of his developing any subsequent pathways is probably completely excluded by the procedure.

Dr. Scott's report was an extremely interesting and honest one and one which I hope will encourage others to follow.

DR. LEO M. DAVIDOFF: When you talk of essential hydrocephalus, you are talking of a large group of different types of conditions. Within the last six weeks we have had two infants under one year of age enter the hospital with enlarging heads; one proved to have a large papilloma of the choroid plexus, and the other a craniopharyngioma. Those two lesions are not common at this age, but tumors producing a picture similar to hydrocephalus must be kept in mind.

When you eliminate conditions such as tumors and congenital abnormalities producing symptoms similar to hydrocephalus, you get down to a group of cases that Dr. Scott and the others have been talking about. You still have two varieties mentioned: the communicating type and the noncommunicating. You will notice Dr. Scott's figures show 21 of the communicating type in his series as against 8, I believe, of the noncommunicating type. This, I think, is the clinical experience of all neurosurgeons, in spite of the report from Dorothy Russell, based on postmortem pathological material, that the majority of them are cases with obstruction somewhere along the ventricular system.

The exact pathological nature of the hydrocephalus is not well understood, and it is my firm conviction, although I have still to prove it, that the reason that communicating hydrocephalus exists is because there is an inadequacy or a complete failure of the formation of arachnoid villi. The degree of hydrocephalus and rapidity with which it progresses from infancy on, perhaps even from uterine life on, depends on how inadequate the arachnoid villi are. The

reason this has not been proven is that it would require a long study of many specimens of normals as well as hydrocephalics to prove the point. I hope some day that work can be carried out.

The success of treatment of these cases depends, however, on the degree of failure of the mechanism to work. For example, a good many years ago the late Dr. Marriott was able to report some excellent results with the simple use of diuretics, such as theobromine sodiosalicylate. That will not happen in a case with the hydrocephalus advancing very rapidly in which the inadequacy is very great. On the other hand, if one has a child in whom the balance between fluid formation and absorption is very slight, then a small amount of help, such as a diuretic can produce, will push him over to the proper side of the scale and with some care on the part of the mother the child can have an arrest of the hydrocephalus.

It is the next stage, that is, cases that are still wild but yet not properly controlled by diuretics, that will do very well if one removes only a single choroid plexus. We have a number of cases in our series in which only a unilateral choroid plexus was done and the hydrocephalus was arrested. We have some—and the majority of our cases were treated by choroid plexectomy—in which a bilateral choroid plexectomy has produced the desired results. There are complications with plexectomies, too. These patients fairly frequently develop postoperative epilepsy, which is disagreeable. A few years ago we found two of them who had developed postoperative subdural hematomas. On the other hand, when we looked up our material, we found a case where we had done a peritoneal anastomosis which had developed a subdural hematoma. This was presumably because of the separation of the cerebral cortex from the under surface of the dura, resulting in a tearing of a crossing vein and the foundation of a subdural hematoma. In the literature we found a similar case reported by Anderson. So this is a complication which need not be ascribed exclusively to choroid plexectomy.

When it comes to the noncommunicating type, I cannot see why anybody would take a tube all the way from the ventricle down into the lumbar space, and from there into the peritoneal cavity, when nature has provided a perfectly adequate tube in the form of the spinal subarachnoid space, which can be utilized for conducting the fluid much more easily, and also a "tube" which will grow with the patient. So the only sensible thing to do, which Dr. Ransohoff has already mentioned, is to do a Torkildsen procedure; then, if necessary, a peritoneal anastomosis.

I would advocate doing the Torkildsen procedure first in the obstructive types, and then the secondary procedure later on. We have more or less worked out a method of dealing with these cases; namely, that if the peritoneal cavity shunt fails, then we do a ureteral shunt. We do not do the ureteral anastomosis primarily because of the very reason that Mattson, who does this regularly, nevertheless admits, that the patient loses a kidney and the electrolytes go into the urine and are eliminated from the body; so you have to be constantly worried about that. The same may be said about the shunt from the ventricle into the mastoid cells, which has been advocated by the Mayo Clinic, and which results in the discharge of the fluid into the nasal passages, where retrograde infection takes place, just as retrograde infection can take place from the urinary bladder into the subarachnoid space.

As you see, there are innumerable problems in these cases of hydrocephalus. But when you see a child, perhaps one out of 5 or 6 or 10 who might otherwise have died and who is restored to normal health, as you frequently do see them, it is worthwhile experimenting with all the others for the sake of that one.

Dr. John E. Scarff: It is very refreshing to hear a paper such as the one Dr. Scott and his associates have presented to us today. It is a healthy and wonderful thing to have an enthusiastic worker in a pioneer field analyze his experiences and results with an open mind, acknowledge his problems and his failures, and discuss them in a simple and direct manner with his colleagues. That is the way truth is established and progress is made.

I might say that I have had a similar happy experience with Dr. Ransohoff, who has worked alongside of me at the Neurological Institute upon this same old problem of hydrocephalus, and who has just finished his discussion of Dr. Scott's paper. It is perfectly true, as he has intimated, that I have experienced comfort on many occasions after I have failed in the treatment of hydrocephalus by my own favored methods to be able to say to the patient's family that I have a friend who has a different and excellent method of treating hydrocephalus, and in quite a number of cases he has been able to salvage these youngsters after I had failed.

Review of 1,000 Patients with Head Injuries. Dr. Axel K. Olsen, Dr. Alexander W. Ulin (by invitation), and Dr. Hubert L. Rosomoss (by invitation).

The charts of 1,000 patients with head injuries of varying degrees of severity admitted to the hospital over the years 1945-1950 were reviewed and the results discussed.

A total of 430 were found to have no evidence of brain involvement and the injuries consisted of extensive scalp lacerations and facial injuries, including contusions and fractures; 570 had varying degrees of cerebral injury; 440 had concussions only, with no mortality. Of these, 314 had no other head injury and 128 had associated skull fractures. Another 128 had severer brain injury. Of these there were 38 subdural hemorrhages, of whom 63% died; 11 epidurals were found in this group and 81% died. Two combined subdural and epidural hemorrhages were found and both patients died.

The total mortality rate was 7.4% but when this is carried down to the 215 patients with multiple types of head injury (contusion, laceration, subdural, epidural), the mortality is 29%.

Extracerebral complications were found to be a serious factor in increasing the death rate, and among these the most frequent and most serious were to be the respiratory complications. Chief of these was airway obstruction due to retained secretions, pharyngeal relaxation, laryngeal edema, etc. Thirty of these were found and of these, 20 were tracheotomized. Of the 30, there were 24 who died. The six survivors were all tracheotomized.

Abnormalities of the neurological examination were found in all 570 of those with cerebral involvement. Unconsciousness alone was found in the 442 with concussion. Of the remaining 128, there were 88 with additional neurological abnormalities.

Noteworthy was the fact that of the patients with cerebral injury and skull fracture 26.1% died and of those with cerebral injury and no skull fracture 5.7% died.

It was concluded that operative exploration was indicated for all patients with deepening or prolonged coma, with progressive neurological signs, and for many patients with neurological signs on admission in whom no history was obtainable.

DISCUSSION

Dr. Peter G. Denker: In Bellevue Hospital some years ago we also reviewed a series of 1,000 cases with approximately the same mortality experience. I was, however, struck by a few points in the paper which raised questions in my mind.

I found it hard to understand, for instance, how in all 442 cases which were listed as "with concussion," all these people were recorded as having been in coma and yet none of them had any neurological signs. In our experience, if a patient is brought in with a concussion severe enough to put him into a coma, out of a group of approximately 400 cases we would expect to find positive neurological findings in a considerable percentage of cases.

I also noticed the discrepancy, which Dr. Olsen himself pointed out, between the roughly 25% mortality in the cases of brain injury in which a fracture of the skull was also present and the approximately 5 or 6% in the uncomplicated cases of brain damage without associated skull fractures.

I wonder whether that diagnosis of skull fracture was made only by x-ray. I did not notice that lumbar punctures were done in those cases. It is common knowledge that if you rely on the x-ray alone in basilar skull fractures you will find them in only 50% or so of the cases, whereas if you do a lumbar puncture it will be diagnostic in a greater percentage of cases. Perhaps that might explain the large disparity between the two groups.

Another item which seemed to me as somewhat contrary to our experience was the question of inequality of the pupils. In the author's cases of subdural and epidural hemorrhages, he noted pupillary inequality in approximately 10% of the cases. I thought that seemed rather a low figure. In our experience I would say that we found such inequality of pupils in perhaps 50 or 60%, and this was a great help in diagnosing the side of the focal lesion.

Dr. Olsen's thought about tracheotomy was, in my opinion, one of the most constructive in the entire paper. I would like to know a little more as to the criteria he uses in making him decide to do a tracheotomy. In some cases I noted it was performed for respiratory obstruction, yet not in others; roughly, he did it in 20, but not in the other 10. In head injuries, the respiratory obstruction is often secondary to brain stem damage, yet the contrasting series of figures which he showed were impressive. There were 6 people out of 20 whose lives were saved in that

tracheotomized group, whereas in the other group, I presume of similar severity, 10 out of 10 died. It may be that this is a real contribution. It may be a procedure worth doing more frequently.

There is only one additional thought I would like to present, and that is the advisability of performing a lumbar puncture in these cases for diagnostic and medicolegal purposes. From a treatment standpoint I do not think it is of much help, yet I do not think any harm is done in taking off a few cubic centimeters of spinal fluid. One of our "headaches" in these cases is what happens two and three years later, when the lawyers have entered into the picture or compensation claims have arisen. It then becomes very important to have something definitive to pin your diagnosis to, in black and white. For that reason we like to do it. We often pick up evidence of a fractured skull, as I indicated before, when the x-ray has been normal. Furthermore, on electroencephalograms, which we frequently take, we often find abnormalities, especially in the early stages, which may disappear a few months later. In fairness to the patient, as so many of these cases end up in litigation, I think this a valuable and practical procedure.

DR. FRANCIS ECHLIN: A number of years ago I reviewed 70 subdural hematomas. Of those 70 there were 48 with unequal pupils at the time of operation, an inequality of the pupils on the two sides. In 24 cases the pupil was larger on the side of the hematoma, and in 24 it was larger on the side opposite the hematoma. In 75% of cases, however, where there was a really large pupil, it was on the side of the hematoma.

Another type of head injury are those with epidural or intracerebral hematomas. They occurred in about 1 or 2% of the severe head injuries. From these statistics it seems that about 7% of severe head injuries have an intracranial hematoma that requires surgery. Most of the remaining cases require only good common-sense nonoperative care.

Only a very small number of acute head injuries are benefited by operation in the first few days after injury. The cases benefited are those with epidural and intracerebral hematoma, and on occasion a case of acute subdural hematoma. Ninety per cent of the patients operated on for acute subdural hematomas in the first 24 hours die. These patients die of their associated brain injury, and the subdural hematoma as a rule is incidental, even though it is large.

There is no question that you can put a good deal of fluid into the subdural space and the patient will show very few symptoms. In other words, one can accommodate to an acute subdural hematoma, but these people who die in the first 24 or 48 hours do not die of their subdural hematoma; they die of a severely damaged brain.

One-quarter of our patients with subdural hematomas were operated in the first six days and 74% of them died. Half of the entire group of subdural hematomas, approximately 150, required surgical intervention on the 7th to the 31st day after injury, and the mortality in that group was only 22%. It dropped from 74% on the sixth day to 22% thereafter. In other words, 78% survived in the group operated more than six days after the injury.

In the truly chronic group, those after 31 days, the mortality was approximately the same, around 22%.

The cause of death in a majority of these patients operated on in the first week after injury is a diffuse brain injury or petechial hemorrhages in the brain stem. This is particularly true in the first few days after injury. After the sixth postinjury day a patient with a subdural hematoma will usually survive if he is operated on before he is allowed to go into deep stupor or coma. The timing of operation is important. If he is allowed to go into coma or deep stupor, the mortality goes up remarkably, and most of our cases in the so-called subacute group after the sixth day or in the chronic group died because they were in coma or stupor at the time of operation.

DR. AXEL K. OLSEN: Dr. Denker, the word coma was probably used wrongly. It probably should have been unconscious.

The skull fractures were x-ray diagnoses.

The pupillary inequality I could not answer myself.

The tracheotomy is done as soon as we are sure that the patient does not have a good airway by the ordinary methods. The 10 patients that were not tracheotomized were treated before we decided to use this method. They were treated otherwise. After we saw the bad results with this method, we decided the tracheotomy was the best.

Cephalic Tetanus. Dr. Nathan S. Schlezinger and Dr. Luis P. Sanchez-Longo (by invitation).

A 5-year-old girl with the syndrome of cephalic tetanus is described and represents only the second case to be reported in the American literature in which tetanus remained limited to the head. The conspicuous neurological manifestations consisted of trismus, right facial spasm, and paralysis in the distribution of the left abducens and facial nerves. A noteworthy recovery was obtained in this case and serves as a basis for the consideration of treatment in such instances. The literature is reviewed with special reference to pathogenesis.

DISCUSSION

Dr. Herbert L. Martin: The major part of Dr. Schlezinger's paper (which I have already had the pleasure of reading) is an excellent review of the pathogenesis of tetanus, emphasizing some important recent work done at Guys Hospital in London, by which it seems to have been conclusively proved, as we originally thought, that the toxin is transmitted along the peripheral nerves to the central nervous system.

I should like to make just two more minor points. First, in the treatment of this disease, aside from the specific measures taken and aside from maintaining an adequate airway, the greatest problem is to prevent the rigidity and convulsions that occur. I have had the opportunity to use mephenesin (Tolserol) in this situation with very good effect. Our experience agrees with the literature in that the oral and intramuscular route is far less satisfactory than the intravenous route of administration. Using a continuous intravenous drip of 2% solution of mephenesin, prolonged muscle relaxation and a greatly reduced incidence of convulsions can be obtained without significant side-effects.

Finally, the immunity that develops after an attack of this disease is at best poor, so that part of the treatment of this condition should be active immunization of the patient before discharge from the hospital. Admittedly, recurrent tetanus is very rare. There are only 50 cases in the world literature and since I observed the 7th case in this hemisphere, you can see that the problem is not great. The greatest danger of recurrence would seem to lie in military situations, or among those in our civilian population subject to recurrent inoculation of tetanus spores, such as drug addicts.

News and Comment

NATIONAL TRAINING LABORATORY IN GROUP DEVELOPMENT

On the basis of nine years of pioneering research and experience in the relatively new field of training leaders in the skills and understandings necessary for developing effective groups, the National Training Laboratory in Group Development will hold two three-week summer laboratory sessions at Gould Academy, Bethel, Maine. The dates will be from June 19 through July 8, and from July 17 through Aug. 5, 1955.

Approximately 125 applicants will be accepted for each of these two sessions. Persons involved in problems of working with groups in a training, consultant, or leadership capacity in any field are invited to apply.

The purposes of the training program are fivefold: to develop sensitivity to the existence and nature of the dynamic forces operating in the small group; to develop self-insight into the effects of one's behavior on others in a group; to gain skills in operating more effectively in a group; to gain understandings and skills for working in larger social units such as organizations and committees, and to develop skills of using scientific methods in social problem-solving.

The training program is organized so that each trainee group is enabled to use its own experience as a laboratory example of group development. Group skills of analysis and leadership are practiced through the use of role-playing and observer techniques. Concentrated clinics give training in the skills of the consultant and the trainer in human relations skills. Training groups explore and experience the role of the group in the larger social environment in which it exists. Finally, a major portion of the last week of the laboratory is spent in specific planning and practicing application of laboratory learnings to back-home jobs.

A special project concerned with the development of understandings and skills of human relations training will be instituted this year for a selected group of delegates

The laboratory research program in group behavior and training methods is an important part of the training, and the use of research tools which are within the range of the laboratory training program is incorporated into the curriculum.

The NTLGD is sponsored by the Division of Adult Education Service of the NEA and by the Research Center for Group Dynamics of the University of Michigan, with the cooperation of faculty members from Boston University, the universities of California, Chicago, and Colorado, Cornell University, the University of Illinois, the Ohio State University, the University of Texas, Wayne University, Grinnell College, Michigan State College, Teachers College at Columbia University, and other educational institutions.

ANNUAL MEETING OF THE AMERICAN ORTHOPSYCHIATRIC ASSOCIATION

The American Orthopsychiatric Association will hold its 32d Annual Meeting at the Hotel Sherman, Chicago, on Feb. 28, March 1 and 2, 1955. This is the first meeting of the Association in Chicago since 1949.

Approximately 100 scientific papers will be presented by psychiatrists, psychologists, social workers, educators, sociologists, and anthropologists. There will be all-day sections on Childhood Schizophrenia, Child Development, and Psychotherapy with children. Visual material of

specific use in mental health education will be presented for two days of the meeting. Twelve workshops are planned as part of the program. Numerous technical and commercial exhibits will be on display.

Papers, symposia, and round tables will discuss a wide range of orthopsychiatric interests, including adolescence, intake, juvenile delinquency, testing, use of the clinic team, research, treatment of psychosomatic disturbances, mental health in the community, rehabilitation, desegregation, and other related material.

The American Orthopsychiatric Association, founded in 1924, is an interdisciplinary association of psychiatrists, psychologists, social workers, and members of allied fields, including education, anthropology, and sociology. Its members come from all parts of the United States, Canada, and abroad.

Officers for the current year are: Simon H. Tulchin, New York, president; Elizabeth H. Holmes, Boston, vice-president; Jessie Edna Crampton, Brooklyn, N. Y., secretary; William S. Langford, M.D., New York, treasurer; Hyman S. Lippman, M.D., St. Paul, past president; Gilbert J. Rich, M.D., Roanoke, Va., David Shakow, Ph.D., Bethesda, Md., Mary C. Sumner, Winston-Salem, N. C., Directors. Editor of the Journal is George E. Gardner, M.D., of Boston. President-elect is Exie E. Welsch, M.D., New York.

Inquiries about the program, reservations, exhibits, and other matters should be directed to Dr. Marion F. Langer, American Orthopsychiatric Association, 1790 Broadway, New York 19.

UNIVERSITY OF CALIFORNIA EXTENSION

University of California Extension will make an advanced course in Techniques and Application of Hypnosis available to Long Beach doctors late in January, according to Thomas H. Sternberg, M.D., Head of the Division of Postgraduate Medical Education at University of California at Los Angeles.

The fourth-floor staff conference room at the Veterans Administration Hospital in Long Beach will be the classroom for the meetings on Jan. 27 from 2 to 5 p. m.; Jan. 28, 9 a. m. to 12 p. m., and 2 to 5 p. m., and Jan. 29, 9 a. m. to 1 p. m., and 2 to 5 p. m.

The course will be conducted on a clinic plan. Cases will be presented at each session involving problems of diagnosis and therapy. The psychological aspects of the cases will be discussed and therapeutic plans will be formulated, although actual treatment will be carried out by the hospital staff, according to Roy M. Dorcus, Ph.D., of U. C. L. A., who is chairman of the course.

With enrollment limited, doctors interested are invited to apply to Dr. Thomas H. Sternberg at the University of California Medical Center, Los Angeles 24.

THE NATIONAL FOUNDATION FOR INFANTILE PARALYSIS

The National Foundation for Infantile Paralysis announces the availability of a limited number of fellowships to psychiatrists who are interested in the emotional problems of the physically handicapped, particularly of the poliomyelitis patient with respiratory difficulties.

These fellowships are awarded as a part of the program of professional education of the National Foundation, for which more than $19,000,000 in March of Dimes funds have been appropriated since 1938.

In order to be eligible for these fellowships, physicians must have completed two years of graduate training in psychiatry acceptable to the American Board of Psychiatry and Neurology, be United States citizens (or applicants for citizenship), and be in sound health.

The applicant must propose a program of study to be undertaken in a center concerned with rehabilitation of the physically handicapped which has affiliations with an approved department of psychiatry. The training of the Fellow in the application of psychiatric concepts and methods

to the treatment of the physically handicapped must be supervised by the department of psychiatry. An opportunity for working with poliomyelitis patients with respiratory difficulties should be available.

Selection of candidates is made on a competitive basis by the National Foundation's Clinical Fellowship Committee. Appointments will be made for one year but may be extended upon recommendation of the Committee.

Financial benefits will be determined by marital status and number of dependents. Stipends range from $3,600 to $7,000 a year.

Applications received by Dec. 1 will be considered in February; if received by March 1, they will be considered in May; if received by Sept. 1, applications will be reviewed in November.

For further information and application forms, address The National Foundation for Infantile Paralysis, Division of Professional Education, 120 Broadway, New York 5.

THE MOUNT SINAI HOSPITAL, NEW YORK

A program for training in child psychiatry has been in operation in the Child Psychiatry Division of the Department of Psychiatry of The Mount Sinai Hospital, New York City, for some years. It is now partially supported by the United States Public Health Service. The Division is a member of the American Association of Psychiatric Clinics for Children, which has also approved it for fellowship training in child psychiatry.

The program includes supervised work with premature and normal infants; psychosomatic and psychiatric problems of hospitalized and ambulatory infants and children; parent guidance and treatment; long-term clinic treatment of childhood psychoses, psychoneuroses, and behavior problems, and adolescent problems. The team approach with psychiatric case work, psychology, and pediatrics as well as a psychodynamic psychoanalytic orientation is stressed.

An honorarium of $3,000 for first year and $3,600 for second year fellowships is offered. The prerequisites include a minimum of two years' approved psychiatric training. Applications for fellowships should be filed before Feb. 1, 1955, with Dr. M. Ralph Kaufman, Director, Department of Psychiatry, The Mount Sinai Hospital, New York 29.

Books

Atlas postmortaler Angiogramme. By Dr. J. Schoenmackers, Apl. Professor für pathologische Anatomie, und Dr. H. Vieten, Dozent für medizinische Strahlenkunde. Price, $13.55. Pp. 203, with 145 illustrations. Georg Thieme, Diemershaldenstrasse 47,(14a) Stuttgart-O (American Zone). American agent, Grune & Stratton, Inc., 381 4th Ave., New York 16.

Postmortem angiography permits visualization of the vascular system in humans in whom autopsy can confirm the absence or presence of disease. It provides thus not only normal controls but angiograms of conditions rarely seen in practice, or in which angiography is rarely done or contraindicated. Conclusions as to circulation in living patients are rarely possible, however. Barium sulfate or other heavy metal salts in solution were injected into the subclavian artery or other vessel, and x-ray photographs made.

After discussing the technical details, limitations of the method, general findings, and the causes of changes seen, the authors show illustrations of angiograms of the lungs, brain, heart, kidneys, trunk, fetus, portal system, and the systemic venous circulation. In each instance normal circulation is presented first, followed by pictures seen in various diseases. The text under the picture gives the pathologic-anatomic diagnosis at autopsy, description of the angiographic findings, and interpretation of the latter in terms of the former. Each section is summarized in German, English, French, and Spanish, with figure references to important points in each summary.

Some of the pictures include avascular fields and pseudoincrease in pulmonary vessels in bronchiectasis and pneumothorax; pseudoincrease of arteries of the brain in heart disease; anastomoses in coronary sclerosis; avascular areas in kidney infarction; vascularization of the pregnant uterus; intercommunication of heart chambers in thoracopagus, and portacaval and portapulmonary anastomoses. Basic book references are given, especially for angiograms of different organs done in vivo. The index cleverly gives both figure numbers and page numbers on the same line for easier search.

This book is one of a series of atlases of normal and pathologic anatomy as seen by roentgenography. Directed at the anatomist, pathologist, and clinician, it should be of value to anyone who has to interpret angiograms of living patients, for the pictures are well reproduced, and the text clear.

The Concept of Schizophrenia. By W. F. McAuley. Price, $3.75. Pp. 145. Philosophical Library, Inc., 14 E. 40th St., New York 16, 1954.

The author reviews the concept of schizophrenia from the pre-Kraepelinian days to our time. He discusses classification and the physiological, dynamic, hereditary, and social factors concerned in the concept as well as the diagnosis and treatment of schizophrenia. Extreme fairness is maintained in holding no special brief or in expressing an overcritical or accepting attitude toward any of the conflicting points of view. In a few concluding remarks the author does plead for a broad viewpoint, "The schizophrenic mind is one that has not adapted itself to the social environment." It is this stressful environment that the author believes needs study.

This book represents the best available summary statements of the manifold concepts of schizophrenia. There is an excellent bibliography and index.

The Analysis of an Obsessional. By R. W. Pickford. Price, $4.00. Pp. 234. W. W. Norton & Company, Inc., 101 5th Ave., New York 3, 1954.

Presented in this volume are selected and abstracted notes containing dreams, associations, and interpretations from the analysis of an obsessional that lasted only 80 sessions spread over 18 months. This material would correspond to five, or at the most six, months of so-called classic analysis. That a favorable result, however, was obtained in this case could be verified by the fact that the patient continued to function well several years after the termination of therapy.

The author not only tells what transpired in his analytic sessions but uses the material to discuss analytic theory and procedures in general. There is a pattern to the material of the analysis and of the general discussion that indicates the author's focus on the sexual problems of his patient. One misses the interest in the problems of growth and development of ego functions. It can only be concluded that the actual treatment was therapist-directed and is the basis for its short time span. This is not to decry such psychoanalytic psychotherapy, for it has great value and effectiveness in some cases. But it should be recognized for what it is.

Finally, the author should be identified as a nonmedical psychologist working in Scotland. There is a good index and a brief bibliography.

The Collected Papers of Otto Fenichel: Second Series. Collected and edited by Drs. Hanna Fenichel and David Rapaport. Price, $6.50. Pp. 374. W. W. Norton & Company, Inc., 101 Fifth Ave., New York 3, 1954.

As for the first series, the editors should be appreciated for their task and the publisher complimented for his cooperation in this venture. Each of the 27 papers is a delight to read and study, which all analysts and dynamic psychiatrists should do. They are all alive with tremendous vitality and valid concepts, and have not lost their significance through the passage of time. The book is most highly recommended.

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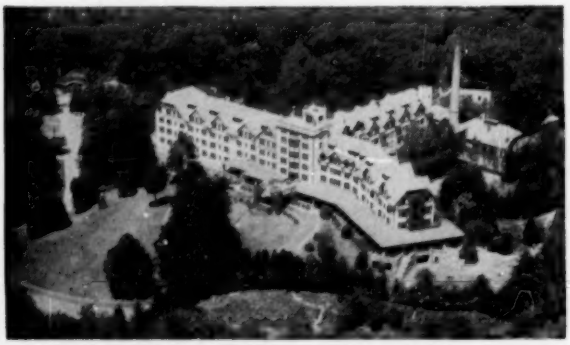

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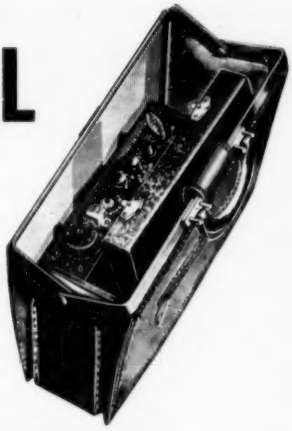

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